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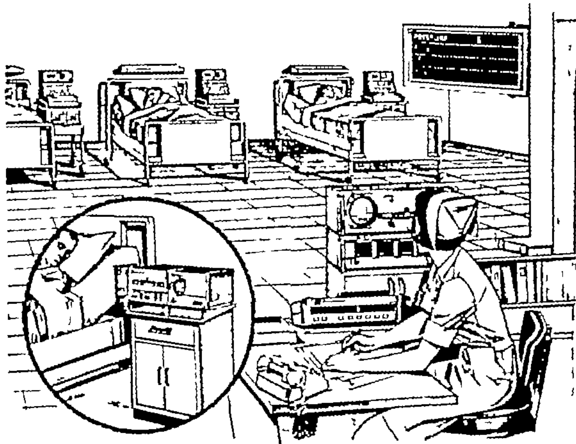
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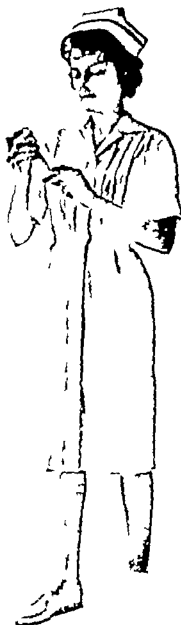
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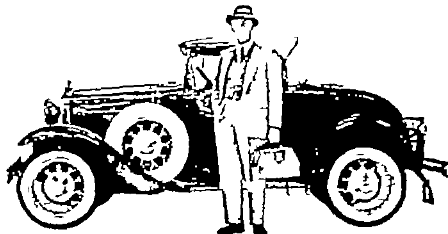
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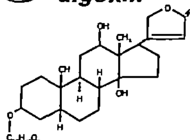
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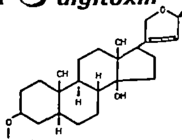
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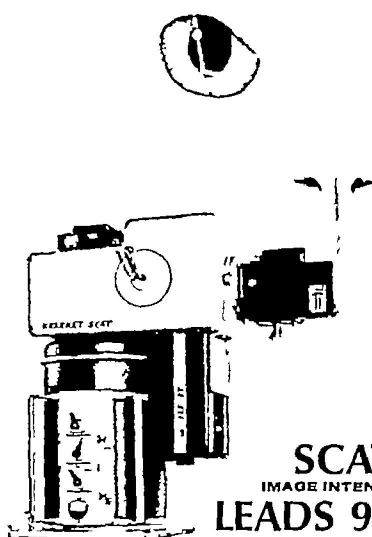
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American Heart Journal

January 1966 Volume 71 Number 1

Editorial

The prevention of strokes

*John Marshall M.D.**
London England

The occurrence of a completed stroke must always be regarded as a major setback in the life of a patient. Inevitably there is some degree of brain damage and although vigorous rehabilitation can do much to minimize the effects, the majority of patients are left with some disability which may be of considerable degree. Therefore, the prevention of completed strokes must be given high priority in the practice of those concerned with cerebrovascular disease.

Our knowledge of the basic causes of degenerative vascular disease is as yet fragmentary and much work remains to be done on the pathogenesis of atherosclerosis before we can hope to prevent those vascular changes which are ultimately responsible for the completed stroke. Nevertheless, there are at the present time interventions open to the physician which will make a significant contribution to the prevention of completed strokes. These can be classified under three broad headings: the eradication of sources of emboli, the investigation and treatment of transient ischemic attacks, and the management of hypertension. These three areas of endeavor will be discussed in turn.

The risks of embolization in certain conditions, such as atrial fibrillation, myocardial infarction, cardiomyopathy, and endomyocardial fibrosis, is well recognized but the extent of the threat to the nervous system is not always fully appreciated. In unselected series of completed strokes, embolization is the cause in from 5 to 10 per cent of cases.[1,2] Alternatively, when seen from the cardiac standpoint in cases of mitral stenosis giving rise to emboli, 75 per cent go to the cerebral circulation.[3] In many of the cases of cerebral embolism it is already known that the patient suffers from cardiac disease, but it should be remembered that in the case of mitral stenosis as many as 12 per cent of patients may first present because of cerebral embolism.[3] The prevention of the first embolus in this latter group is clearly impossible, except perhaps by routine examination of people in positive health. Yet even after the first embolus, there is scope for prophylaxis, for further embolization is likely to occur in about 60 per cent of cases.[3] Moreover, whereas the mortality from a first embolus is about 7 per cent, that from further emboli is about 27 per cent.[4]

Although the exact place of anticoagulant therapy in the management of cerebrovascular disease is still the subject of

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some disagreement there is practically universal acquiescence in its value in cases of cerebral embolization. The evidence in support of this is considerable[2,3] and there cannot be any real doubt upon this question. Ideally, treatment should begin before the first embolus occurs, hence the necessity for instituting anticoagulant therapy in all cases in which a potential source of emboli is known to be present until such time as that source can be eradicated whenever this is practicable. The importance of this was shown by a series of 105 patients with mitral stenosis in whom valvotomy was deferred because symptoms were trivial or absent. Over a period of 4½ years, 15 patients experienced a cerebral embolus, five of which proved to be fatal.[4] If embolization has already occurred, treatment should be started immediately with heparin, to be followed by coumarin or indanedione derivatives. It must be continued until all danger of further embolization is past.

The importance of transient ischemic attacks (T.I.A.s) in the field of cerebrovascular disease cannot be exaggerated. These short-lived disturbances of neurological function frequently give warning that a completed stroke is impending. This danger is much greater when the T.I.A.s are occurring in the distribution of the carotid artery and its branches than when the vertebrobasilar territory is involved. In a series of patients with completed strokes which had been preceded by transient ischemic attacks in the carotid territory, no less than 76 per cent had experienced only one or two T.I.A.s beforehand, 47 per cent occurring in the month prior to the stroke.[5] The appearance of T.I.A.s in the carotid territory is, therefore, a signal for immediate action.

The first step must be to ascertain the immediate cause, for there are a variety of these. Anemia and polycythemia[6] have both been incriminated and can be eliminated at the first examination of the patient by appropriate hematologic examination. Transient fall in blood pressure may also be responsible.[7] This cause can usually be detected from the history of the attacks, their occurrence against a background of lowered cardiac output, as in myocardial infarction, or fall in blood volume as in severe hemorrhage is suggestive; alternatively, the patient may be receiving hypotensive therapy which is poorly controlled. Correction of these factors will stop the attacks. Transient hypertensive crises may also occur[8] and give rise to focal neurological symptoms and signs instead of the more generalized disturbance of cerebral function usually associated with hypertensive encephalopathy. Such patients have malignant hypertension or show evidence of being on the verge of developing it. Immediate control of the blood pressure is essential.

These four conditions, although readily detected at the first examination, account for only a minority of cases of T.I.A.s. For the remainder, four-vessel angiography is essential for a proper assessment of the case. There may be clues in the history as to what is likely to be found. Thus, a past history of pain in a cervical root and a story that the T.I.A.s tend to occur whenever the patient turns his neck suggests intermittent compression of the vertebral artery by osteophytes due to cervical spondylosis.[9] The association of attacks in the vertebrobasilar territory with use of the upper limbs and the finding of a difference in the level of blood pressure in the two arms raises the question of the presence of a subclavian-steal.[10] The presence of a bruit over the bifurcation of the carotid artery in the neck indicates that a stenosis may be present. These and other stenotic and compressive lesions of the carotid or vertebrobasilar arteries can only be diagnosed accurately by angiography, which must therefore be carried out as a necessary step toward rational treatment. This may be by means of surgery, as in endarterectomy or the removal of osteophytes, or by the restriction of neck movements through the use of a collar.

Alternatively, anticoagulant therapy may be instituted. The justification for this is the increasing evidence that atherosclerotic plaques in the great vessels may provide a site for the formation of fibrin-platelet or cholesterol-debris emboli which subsequently impact in cerebral or retinal vessels.[11,12] In addition, there is clinical evidence from controlled trials of the value of anticoagulant therapy in transient

ischemic attacks.[18,19] Therapy should be continued for at least a year after the last attack.[20]

The third way by which it may be possible to forestall the development of a completed stroke is by the proper management of hypertension. Although hypotensive therapy rapidly found a place in the management of uncomplicated hypertension and that giving rise to cardiac symptoms, its use in patients with cerebrovascular disease has been approached with considerable diffidence. This probably was due to the widespread belief that "cerebral thrombosis" is caused by low blood pressure. This, in turn, was due to a failure to distinguish between those cases in which cerebral infarction develops in association with a sudden and profound fall in blood pressures, as may occur in myocardial infarction and gastrointestinal hemorrhage, and those cases of uncomplicated cerebral infarction in which the blood pressure is, on the average, higher than that of the normal population.[21]

Cerebrovascular accidents are a common cause of death in patients with untreated hypertension, and the incidence of this cause may be considerably reduced by the use of hypotensive therapy.[22,23] This beneficial effect on mortality has been shown to be present even when the patient has already experienced a stroke.[24] Furthermore, there is a significant reduction in the further incidence of nonfatal strokes. There can be no doubt, therefore, as to the value of lowering the blood pressure in the prevention of strokes. Certain points must be observed when giving hypotensive therapy to patients with cerebrovascular disease. So severe a reduction in blood pressure as is necessary for the young man with malignant hypertension should not be sought; a diastolic level of about 100 mm. Hg is satisfactory for the cerebrovascular patient. Drugs which have a marked postural hypotensive effect should be avoided. The patient must be carefully instructed about the advisability of taking some gentle exercise on the bed before first rising in the morning and about the need to lower the head immediately if ever he should experience hypotensive symptoms.

Although our understanding of cerebrovascular disease is far from complete, we nevertheless, already have some means by which we can reduce the incidence of its most devastating effects. Until such time as we can eliminate the basic causes of degenerative vascular disease, the careful application of these means will prove to be rewarding.

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Clinical communications

Transvenous electrical pacing of the heart

Results of 96 insertions in 78 patients

*Yusuf Ziya Yuceoglu, M.D., F.A.C.C.**
Maurice Langer, M.D.
David T. Dresdale, M.D., F.A.C.P.
Brooklyn, N. Y.

The development of techniques for electrical pacing of the heart in the past 12 years has resulted in enormous progress in the management of patients with symptomatic heart block. Cardiac pacemaking was first successfully accomplished in man indirectly by external transthoracic electrical stimulation.[1] Direct methods include stimulation by way of an electrode catheter placed in the heart[2-3] and by wires inserted directly into the myocardium.[4-8] With the low voltage needed for direct stimulation, a miniaturized power pack,[7-1] induction-coupled[11] or radio-frequency pacemaker[12-14] can be permanently implanted surgically. Of the direct methods, transvenous electrical pacing of the heart has been of particular value in the temporary management of symptomatic A-V block that is associated either with Stokes-Adams syndrome or other complications, and occasionally in other disturbances of cardiac rhythm.

Although it has been known for a long time that the heart contracts when stimulated by an electrical impulse, this information was not successfully applied to the treatment of ventricular standstill until 1952, when Zoll[1] reported pacing of the heart by an external transthoracic electrical current. This method has been used widely and successfully. It remains valuable in emergency resuscitation of patients from cardiac standstill as may occur in patients with conduction disturbances, in reflex vagal standstill during anesthesia, surgery, diagnostic procedures, acute myocardial infarction, and after the administration of drugs.[15-18] This method is particularly valuable as an emergency measure in sudden cardiac arrest. Prolonged continuous use is not practical because of the secondary effects of the high voltages required.

Direct stimulation of the heart in clinical practice was first used successfully in 1957 by Weirich, Gott and Lillehei[4] in patients with congenital heart disease who developed postsurgical heart block. Cardiac pacing was accomplished by means of myocardial electrodes inserted at the time of operation and connected externally to an artificial pacemaker. Lillehei and his associates[8,9] later reported the percutaneous insertion of a wire electrode into the right ventricular wall. Callaghan and Bigelow in 1951 by introducing a bipolar or unipolar pacemaker electrode via the

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external jugular vein into the superior vena cava to the right auricular junction near the sinoauricular node were able to show in animal experiments that the heart rate could be controlled by transvenous electrical pacing during periods of standstill. They also demonstrated that the normal sinus pacemaker rate can be taken over by an electrical artificial pacemaker at rates faster or slower than the original sinus rate. The bipolar electrode catheter was found to be superior to unipolar catheters. It was introduced for clinical use by Parsonnet and associates[26] in 1962.

In 1958 endocardial stimulation was achieved by Furman and Robinson in experimental heart block[4] by the use of an electrode catheter inserted transvenously into the right ventricle. Shortly thereafter the method was extended to the treatment of medical heart block associated with Stokes-Adams episodes.[5] Transvenous intracardiac electrical pacing of the heart has since been reported in a larger group of patients with A-V dissociation and Stokes-Adams episodes, congestive heart failure, or ischemic brain syndrome.[11,33] It has also been used for long term therapy.[12]

In this report, transvenous intracardiac electrical stimulation of the heart was used for interim pacing or for short term control of certain arrhythmias. The purpose of this presentation is to report in detail the experience with 96 such temporary catheter insertions in 78 patients.

Material and methods

During the period May 24, 1961, to July 1, 1964, 78 patients, on 96 occasions, had an electrode catheter pacemaker inserted for temporary pacing. Their ages ranged from 48 to 89 years. Only 9 patients were under 60 years of age. Eighty-eight per cent were over the age of 60 years; 17 per cent were over 80 years. There were 43 males and 35 females.

The cardiac diagnosis was arteriosclerotic heart disease (nonacute coronary disease) in 73 patients. Twenty-nine of these patients had complete permanent A-V block; 19 had complete A-V dissociation with transient episodes of either partial heart block or regular sinus rhythm. Twenty-three patients had atrial flutter-fibrillation with complete heart block or extremely slow ventricular response. In some there were transient episodes of regular sinus rhythm with full conduction or atrial fibrillation without heart block. One patient had regular sinus bradycardia with very slow heart rate and Stokes-Adams episodes due to cardiac standstill. One patient had regular sinus rhythm with repeated syncopal episodes due to ventricular flutter-fibrillation. The diagnosis of coronary artery disease was confirmed by postmortem examination in 11 patients. In the remainder the diagnosis was based upon a past history of myocardial infarction or typical angina pectoris. An autopsy diagnosis was made of rheumatic heart disease complicated by arteriosclerotic heart disease in 2 patients, idiopathic myocardial hypertrophy in 1, idiopathic myocarditis in 1, and cor pulmonale with arteriosclerotic heart disease in another.

The most common indication for transvenous cardiac pacing was Stokes-Adams syndrome (Table I). The syncopal mech-

Table I. Indications for transvenous pacemaker in 78 patients

	Number of cases
A-V block associated with Stokes-Adams syndrome	
Ventricular standstill	30*
Ventricular tachyarrhythmia	27†
Ventricular standstill with ventricular tachyarrhythmia	6
Regular sinus rhythm with episodes of ventricular flutter-fibrillation unresponsive to Pronestyl or quinidine	1
Extreme regular sinus bradycardia with Stokes-Adams seizures due to cardiac standstill	1
A-V block with intractable congestive heart failure due to slow rate (low cardiac output)	12
Atrial fibrillation with extreme bradycardia, ischemic brain syndrome, and heart failure	1
Total	78

*Two with severe congestive heart failure; two with severe cerebral ischemia.
†One with severe congestive heart failure.

Table II Results of drug therapy

	Number of patients	Atropine			Digitalis and diuretics			Isuprel (I V and/or sublingual)			Prednisone			Chlorothiazide			Quinidine and Pronestyl		
		N	II	*V*	*N*	*W*	*V*	*N*	II	*V*	*N*	II	*V*	*N*	II	*V*	*N*	II	*V*
Complete A V block with S-A due to cardiac standstill and/or CHF	29	2			4	4	1	7	4	16	3	2	2	4	1	2			
Partial or intermittent block with S-A due to cardiac standstill and/or CHF	7	1				1		2	3	1	2		1	1					
Atrial fibrillation with slow ventricular rate and S-A and CHF	2	1				1		1		1				1					
Slow sinus bradycardia with S-A due to standstill plus CHF	1					1				1									
RSR with episodes of V T severe hypokalemia	1																1		
Totals	40	4			4	7	1	10	7	19	5	2	3	6	1	2	1		

S-A: Stokes-Adams attacks. *I V*: Intravenously. *N*: No effect. *W*: Underlying condition worsened. *V*: Ventricular arrhythmias de novo. *CHF*: Congestive heart failure. *RSR*: Regular sinus rhythm. *V T*: Ventricular tachyarrhythmias.

anism was due to ventricular standstill or ventricular tachyarrhythmia interspersed with attacks of cardiac standstill. Congestive heart failure due to low cardiac output associated with A V block with slow ventricular response was the only indication for cardiac pacing in 12 patients. Other less frequent indications are shown in Table I. Prior and preparatory to repair on 18 additional occasions the transvenous electrode catheter was used in the management of recurrent symptoms due to malfunction of implanted pacemakers.

An attempt was made initially to control symptoms with various drugs in 40 of the 78 patients (Table II).

Electrical stimulation of the heart was obtained by the introduction of a radio-paque electrode catheter through a vein into the right ventricular apex by the standard right heart catheterization technique. A unipolar electrode catheter was used in the first 50 insertions. Goetz[17] bipolar electrode catheters were used in the other 46 insertions. Catheters were all No. 5 French in size except for four which were a No. 9* or No. 6† French especially designed with a lumen for pressure recording 1 cm. proximal to the electrode tip. The cutdown site was the saphenous vein on 56 occasions, the external jugular vein on 28, and an antecubital vein on 12. For the first insertion, veins on the right side were preferred. Arm veins were used only as a last resort.

Patients were all attached to a monitor pacemaker‡ before the procedure was attempted, so that the electrocardiogram could be followed and external pacing of the heart could be obtained in cases of cardiac standstill. A defibrillator was also always available.§ Proper grounding of all equipment was strictly observed.

After the introduction of the catheter a ligature was placed proximal to the incision and around the vein in such a way as not to interfere with the manipulation of the catheter but sufficient to prevent bleeding from the usually high venous

*U.S. Catheter Company, Glens Falls, N. Y.

*U.S. Catheter Company, Glens Falls, N. Y.
†Especially made for us by U.S. Catheter Company.
‡Electrodyne PAB-4 or C 100, Electrodyne Company, Inc., Norwood, Mass.
§Electrodyne C-100 or D-72.

pressure and protect against air embolism when the jugular vein was used. Although air embolism is not very likely to occur in patients with high venous pressure, precautions were taken routinely against this. Either the patient's head rested on the table without a pillow, or the head of the x-ray table was lowered. These simple measures cause venous distention, which facilitates and shortens the jugular venous cutdown time significantly.

After proper positioning of the catheter tip in the right ventricular apex, the proximal end of the wire was then connected to a battery-powered, transistorized pacemaker.* On several occasions the internal pacing connection of the pacemaker monitor was used temporarily. The proximal end of the unipolar electrode catheter wire was connected to the cathode of the pacemaker; the anode was attached through an insulated wire to an indifferent subcutaneously placed electrode which consisted of a [illegible]-gauge steel needle. When the bipolar Goetz catheters were used, the two proximal wires of the electrode catheter were attached to the terminals of the pacemaker without regard to polarity.

After proper cardiac pacing was obtained and heart rate was controlled, the patient was moved into different positions and told to perform forceful respiratory efforts to be certain that the catheter was in a secure position. The catheter was then suitably fixed in position and a sterile dressing applied.

With the catheter in the right ventricle, the voltage necessary to pace the heart was usually less than 1 milliampere. The presence of a constant and continuous one-to-one ventricular response at this current was then a check on proper placement of the catheter. A final increase to 1.5 to 2.5 milliamperes then provided a margin of safety.

The most commonly used pacing rate was 70 per minute, with a range of 65 to 100 per minute. However, in all cases, when it was necessary to suppress an ectopic focus or foci, the lowest rate over 65 necessary to do so was used. Higher rates were also used empirically when there was an increased metabolic need.

*Model No. [illegible] or [illegible], Medtronic, Inc., Minneapolis, Minn.

When the saphenous vein was used, the power pack was placed on the abdomen with elastic straps around the waist and thigh. In jugular insertions, the pacemaker was hung from the neck, with elastic tape holding it onto the chest. When an antecubital vein was used, it was attached to the arm. Gauze padding was placed underneath the pacemaker in order to prevent skin irritation and absorb moisture.

Prophylactic antibiotics were used routinely in almost every patient for 3 days. Penicillin and streptomycin were the drugs of choice. Recently, antibiotics have been omitted on a few occasions without any apparent infection.

Anticoagulant therapy (intravenous heparin) was used after the first 37 insertions.

Results

Immediate satisfactory pacing of the heart was obtained in all patients, except one. This patient, an 55-year-old woman who had severe congestive heart failure associated with acute coronary insufficiency, developed complete cardiac standstill after the catheter had been inserted into the right ventricular apex. Despite attempts to stimulate with very high voltages using a pulse generator, no ventricular response could be obtained. No apparent cause was found at autopsy for this failure. Three other patients died despite resuscitative measures during the procedure but before the catheter could be positioned in the ventricle. These patients were all moribund elderly individuals. An attempt to insert the catheter at bedside without fluoroscopic control was unsuccessful in one of these patients. After this event, no further blind attempts were made.

Duration of transvenous pacing was from 2 hours to 29 days, most commonly 1 to 14 days. Transvenous pacing was continued until optimal clinical improvement was obtained before the patient underwent operation for implantation of a permanent pacemaker.

The effects of prior medical therapy in 40 patients are shown in Table II. All drugs were administered at clinically established therapeutic dosage levels. Atropine, used in 4 patients, had no demonstrable effect. Although digitalis had no effect

in 4 patients the condition of 6 others was made worse. Their cardiac failure increased and attacks of cardiac standstill recurred with one patient developing ventricular tachyarrhythmia which had not been previously present. Of the 36 patients who received isoproterenol 19 developed ventricular arrhythmias. In 5 this consisted of multifocal ventricular ectopic beats in the remainder Stokes-Adams seizures occurred due to ventricular flutter and/or fibrillation The additional episodes of ventricular tachyarrhythmia treated with prednisone and chlorothiazide occurred in patients who were concomitantly receiving isoproterenol. These other agents did not significantly alter the clinical course. One patient with regular sinus rhythm and recurring episodes of ventricular tachyarrhythmia and severe hypokalemia failed to respond to procaine amide and the concurrent intravenous administration of potassium A few patients with heart block had been successfully managed without electrical cardiac pacing during the period covered by this report.

Repositioning of the catheter was required in 19 instances. In 8 instances this occurred with unipolar electrode catheters and in 11 it occurred with the bipolar catheter There were no infections in these cases.

Among the 36 patients who were given anticoagulants one developed a large hematoma at the site of cutdown Another patient developed bleeding at the site of cutdown and widespread ecchymosis. This patient developed thrombophlebitis of the right saphenous vein (cutdown site for transvenous pacing) 10 days after operation and 15 days after anticoagulant therapy was discontinued

In cases in which blood pressures were recorded before and after cardiac pacing a significant change occurred especially in those patients whose heart rates initially were below 50 per minute. After the higher rates of transvenous cardiac pacing there was a significant drop in the systolic hypertension associated with slow heart rates. Diastolic pressures rose to normal levels.

Complications of transvenous pacing are shown in Table III Ventricular tachyarrhythmia requiring defibrillation was

Table III *Electrode catheter complications*

Arrhythmias during insertion	
Ventricular tachyarrhythmias requiring defibrillation	19
Ventricular standstill requiring external pacing	6
Perforation of right ventricular outflow tract	2
Possible perforation of great cardiac vein	1
Repositionings (11 patients)	19
Bleeding	2
Thrombophlebitis	1
Infection	
Local, at phlebotomy site (saphenous)	2
Sepsis	2
Ulcerative bacterial endocarditis (rheumatic heart disease)	1
Death during catheter insertion	4

*Total of 9 patients: 4 times in one patient, and 8 times in another. Both patients survived

the most common problem occurring before the catheter could be successfully positioned in the right ventricle in 9 patients. Of these one patient had to be defibrillated eight times, and another four times. Both survived Once effective cardiac pacing had been established ventricular tachyarrhythmia occurred transiently in only one patient. Ventricular standstill requiring immediate external pacing of the heart occurred on 6 occasions. One patient with regular sinus rhythm with periods of cardiac standstill developed repeated episodes of standstill each time the atrium was touched by the catheter The unusual sensitivity of the atrial wall in this patient was unique in this series. No episodes of cardiac standstill occurred after cardiac pacing had been established

In 2 patients in whom bipolar No. 5 catheters were used one by the jugular route, the other by the brachial route the catheter perforated the outflow tract of the right ventricle after several days of effective pacing These 2 patients suddenly required a marked increase in amperage for effective pacing Although the tip of the catheter was found in the pericardium at the time of operation this did not result in cardiac tamponade or significant bleeding Although cardiac pacing ceased when the pericardium was opened it was readily re-established by pushing the catheter back into the heart. Both patients survived

without further complications. Possible perforation of the great cardiac vein was suspected in one patient because of the low position of the catheter and high amperage required for pacing. After repair of a previously implanted pacemaker, the patient did well.

Significant infection occurred in 5 patients. In 2 this was local, developing at the sites of saphenous vein cutdown. Two developed sepsis. One of these, with a jugular vein cutdown, had staphylococcal sepsis 5 days after insertion. Two days later a permanent pacemaker was implanted and the catheter removed. With large doses of antibiotics the patient recovered. The other patient was an elderly man who was hospitalized with bilateral pneumonia and died with a septic course after 19 days of transvenous cardiac pacing via a saphenous vein cutdown. The fifth patient had severe rheumatic aortic and mitral valvular disease and had undergone several previous permanent implantation procedures. Ulcerative bacterial endocarditis of the aortic valve developed while she was being paced with a catheter inserted through an antecubital vein. Staphylococcus was isolated in all instances. *Pseudomonas aeruginosa* was also present in one case.

Seven patients died after 1 to 9 days of transvenous cardiac pacing. Postmortem examination was obtained in 5 of these patients and in 10 of 15 who died 1 day to 12 months after implantation of a permanent cardiac pacemaker. None of these 15 autopsied cases showed any evidence of endocardial damage which might be attributed to electrode catheter pacing.

Discussion

This study supports the conclusions that have been reported by others[illegible] that transvenous pacing of the heart has proved to be an invaluable method for temporary management of patients with symptomatic heart block. It is also occasionally worth while in disturbances of cardiac rhythm other than A-V dissociation (Table I). Since the occurrence of heart block in the course of myocardial infarction is an ominous development, electrical pacing of the heart should be considered. This has been done with some success by the transvenous method[illegible] and by percutaneous myocardial electrode insertion.[5] In such unusual situations, transvenous pacing should be instituted when ancillary measures fail to restore an adequate rate or fail to suppress a life-threatening ectopic ventricular focus.

Transvenous pacer therapy should be considered primarily for emergency and interim control of the heart rate. With continuous control of the heart rate, Stokes-Adams episodes due either to ventricular tachyarrhythmia or ventricular standstill are eliminated, with concomitant improvement in cardiac, cerebral, and renal function. These benefits are essential for the safe conduct of surgery.

One patient early in this series who was not being paced during operation to repair a defective implanted pacemaker developed a bout of ventricular fibrillation that resulted in brain damage. Since this episode the policy has been to pace all patients undergoing operation for implantation of a pacemaker or subsequent repair. This dual approach of transvenous pacing prior to and continued through implantation of a permanent pacemaker was first reported by Abelson and associates[illegible] and is now widely accepted.[illegible] Although the external pacemaker has been successfully used as the sole support in conjunction with drug therapy during operation,[illegible] it is believed that the use of the transvenous method provides more certain control and results in better clinical improvement, necessary prior to operation. If the cardiac arrhythmia is transient and disappears, pacing of the heart can be discontinued. In patients with acute heart block, every effort should be made to eliminate the causative factors, such as digitalis and rauwolfia intoxication or electrolyte disturbances.

Drug therapy of Stokes-Adams syndrome has recently been reviewed by Landegren and Biörck[illegible] and Bellet.[illegible] Isoproterenol and epinephrine were found by Zoll and his associates[illegible] to be equally effective in dilute solutions given intravenously. More recently, Zoll[illegible] emphasized the effectiveness of intravenous isoproterenol therapy and places reliance on this for interim use rather than transvenous elec-

trical pacing since he believes that the latter is associated with too many complications.

Transvenous pacing had to be instituted after drug therapy proved to be unsatisfactory in 40 patients included in this series (Table II) Although Bellet[38] believes that atropine may be useful because of its blocking action against acetylcholine, it had no effect in 4 patients. Isoproterenol is the usual drug of choice having been shown by Nathanson and Miller[41] to accelerate the ventricular rate in patients with complete heart block. Favorable clinical results have been reported[34-37,39,40] However of the 36 patients who had received recommended dosages[33-37,39-41] of isoproterenol 5 developed episodes of ventricular tachyarrhythmia which was not previously present Too fast administration of isoproterenol may cause ventricular tachyarrhythmias.[42] However serious ectopic ventricular rhythms have been observed with dosages equal to and lower than those effective in treatment.[34] Marked differences in the effect of the drug may occur in the same patient which indicates a change in myocardial responsiveness to the drug from time to time.[34] Clinically safe idioventricular rates produced by isoproterenol in patients with heart block are often insufficient to suppress ectopic centers already present and active. Therefore, Stokes-Adams seizures due to ventricular tachyarrhythmias are sometimes poorly controlled It may be impossible to maintain satisfactory cardiac output with isoproterenol despite its positive inotropic effect,[42,43] unless simultaneous improvement in heart rate is also effected. With low cardiac output, acidosis may develop with further impairment of myocardial contractility cardiac conduction, and responsiveness to sympathomimetic amines.[41,46]

Although initially enthusiastic results were reported with corticosteroids,[41,47] subsequent experience has not been confirmatory.[38] They were found to be ineffective in the 10 patients in this series to whom administered Corticotropin[41] or corticosteroids[38,41] may restore normal A-V conduction in patients with acute myocardial infarction and after open heart operation if partial or intermittent block is due to edema around the bundle. Theoretically corticosteroids may be useful in heart block when myocarditis is the suspected etiology

The good results obtained by Tobian[49,51] using chlorothiazide to lower the serum potassium could not be duplicated in these patients or by others.[34] Poor results with medical therapy have also been noted by others. Portal and his associates[52] found drug therapy to be ineffective in reducing Stokes-Adams episodes In 100 cases of Stokes-Adams syndrome observed at Mount Sinai Hospital Friedberg and associates[53] found the results with medical therapy and external pacemakers or defibrillators to be very poor

Although the primary purpose of digitalis therapy in patients with heart block and congestive failure is to increase cardiac output, the actual effect may be the complex result of a combination of factors. The topic has recently been extensively reviewed by Schwartz and Schwartz.[55] These authors point out that, although excellent results may be achieved in certain situations, great caution must be exercised in order to avoid interrelated toxic effects on the conduction system They also considered digitalis to be contraindicated when Stokes-Adams episodes were due to ventricular tachyarrhythmias, or when seizures occurred during transient heart block and normal sinus rhythm. Once effective cardiac pacing had been established in patients of this series additional benefit could then safely be obtained with digitalis. Muller and Bellet[56] found effective cardiac pacing to be necessary for the successful management of heart failure in heart block.

Thirty-eight patients were treated by transvenous cardiac pacing without initial drug therapy The majority of these patients had repeated episodes of tachyarrhythmia either as the only mechanism or interspersed with attacks of ventricular standstill These patients were so treated because their immediate prognosis was considered to be extremely grave. A single documented episode of Stokes-Adams attack due to ventricular tachyarrhythmia is sufficient indication for electrical cardiac pacing Transvenous cardiac pacing is preferred to drug therapy for C

Adams syndrome due to cardiac standstill, especially in the elderly and when associated heart failure, renal or cerebral manifestations are present. Undue delay in such patients may result in increased morbidity and mortality.

The immediate effect of electrical cardiac pacing has been impressive, as others[illegible] have also noted. Improved hemodynamics[illegible] are reflected immediately in alertness and restoration of skin color. Even coma due to cerebral ischemia has been reversed. Unless myocardial damage is extreme, venous pressure tends to become normal after electrical cardiac pacing, systolic hypertension disappears, diastolic pressure increases to normal levels, and circulation time is shortened. As a rule, a diuresis occurs in the first 24 hours. Clearing of the lungs and relief from dyspnea may be especially dramatic. Azotemia secondary to diminished renal blood flow disappears, although in many of the patients some retention of nitrogen persists because of additional chronic renal disease.

Procaine amide[illegible] and quinidine[illegible] are contraindicated in the presence of A-V block. Quinidine[illegible] is known to increase the refractory period and to slow conduction. In patients with conduction defects its most deleterious effect is probably in increasing the heart block further and depressing the myocardium. Because of this depressant effect on conduction in the ventricles, it further prolongs the refractory period and depresses impulse formation. The danger of using these agents is then probably related either to their slowing action on the idioventricular rhythm or the possible complete suppression of the only ectopic focus available to preserve the ventricular rate.[illegible] A failure to appreciate these facts may result in a fatal outcome. However, these drugs can be safely used to suppress ectopic foci which occur during effective transvenous cardiac pacing. Parsonnet and associates[23] tend to use quinidine when there is any evidence of undue myocardial irritability after the insertion of the electrode catheter. Chardack[illegible] has successfully used procaine amide in myocardial irritability in patients with implanted pacemakers. In such situations an attempt should first be made to obliterate the arrhythmia by increasing the pacing rate. In most of the cases it was possible to suppress the ectopic focus by this simple expedient.

Escher and associates[illegible] found in hemodynamic studies on paced patients that cardiac output increased in all with an increase in the heart rate. The greatest percentage increase occurred at a rate of about 70 with gradually diminishing increments in output as the rates were further increased. They found no further change with exercise at a given rate. The degree of increase may be different in different patients, and optimal rates for maximum increase have been found to vary.[illegible] More recent work suggests that there is rarely any significant increase in cardiac output when cardiac rate is raised beyond 65 beats per minute and that cardiac output can be increased by exercise at fixed rates.[illegible] Less commonly there is a fixed stroke volume and, therefore, rate-dependent cardiac output.[illegible] Clearing of congestive failure has then been noted with higher pacing rates when other measures failed. Clinically, heart rates around 70 per minute are usually adequate.

Repositioning of the electrode catheter has not been a serious problem. This probably was due to positioning of the tip of the catheter against the endocardial surface in the right ventricular apex, where there was less tendency for the catheter tip to become displaced.

The main advantage of the bipolar electrode has been the ability to connect both limbs interchangeably directly to the external battery-powered transistorized pacemaker. With the single-pole types, a frequent cause of secondary failure to pace was dislodgment of the indifferent electrode. Furthermore, pain at the site of this indifferent electrode is quite common at higher currents.[2] Since a subcutaneous needle was used rather than a wire suture, skin infections or irritations at this site were less frequent than reported by Schwedel and Escher.[illegible] The shorter pacing time was also an important factor. According to Parsonnet and associates,[23] the most important advantage of the bipolar catheter is the ability to pace without endocardial contact, thus preventing the complication of endocardial irritation and occasional perforation of the myo-

cardium from the continual pressure of the electrode tip. Perforations, although uncommon have been reported.[11,22,23,27] Schwedel and his associates[2] observed no evidence of necrosis of the tissue or inflammatory reaction despite long term pacing with endocardial contact. No instance of endocardial damage was found despite routine endocardial contact, in the patients here reported on who have come to autopsy DeSantis[22] has also not observed endocardial damage in post mortem studies Although others prefer the catheter to lie free in the right ventricular outflow tract[23] or mid-outflow position or middle of the right ventricle,[21] its continued "freedom" is not secure The position of the catheter in the outflow tract of the right ventricle recommended by Parsonnet and associates[25] may not be ideal. The two ventricular perforations cited were with bipolar catheters. In these instances the tips were found to have slipped from the apex into the right ventricular outflow tract. Experience with the apex application has proved its safety and advantages. There have been no perforations in this area fewer repositioning problems and lower voltage requirements because of continued endocardial contact. Moreover it is rare to have ventricular ectopic beats which commonly occur when the tip is left in the outflow tract. Because of the increased stiffness of the bipolar electrode catheter one must be more cautious in order to guard against perforation, especially when the jugular or brachial routes are used There was no such occurrence in any of the saphenous route insertions despite the greater number done.

The jugular route is by far the easiest and best tolerated by the patients The danger of air embolism has been grossly exaggerated. The route from the arm vein has been used only when other sites were unavailable. Repositioning problems seem to be more common in this group and tension on the catheter is often poorly controlled. It has recently been suggested that the bipolar electrodes may be free in the outflow tract while the tip is in the pulmonary artery.[26] Experience with this placement has not been reported as yet There may be a greater danger of producing pulmonary artery thrombosis with this technique.

Significant infection such as sepsis, related to the electrode catheter was uncommon. No cases of sepsis were reported in Parsonnet's[25] series of 47 insertions in 35 patients. It occurred in 2 of 19 patients with 30 insertions reported by Portal and his associates.[27] Schwedel and associates[21] observed bacteremia 20 times in 17 patients. This was related to repositioning of the same catheter in the same vein in 6 patients. This high incidence of sepsis indicates that long term transvenous cardiac pacemaker therapy with repeated repositionings predisposes to this serious complication

Ventricular tachyarrhythmias requiring countershock is not an uncommon occurrence during the procedure before proper positioning of the pacemaker catheter Ventricular standstill requiring external cardiac pacing occurs less often In 47 instances of catheter use Parsonnet and associates[25] also observed seizures in 17 cases.

There appears to be no advantage in anticoagulant therapy There was no difference in voltage requirements or any evidence of thromboembolic phenomena in those who were not anticoagulated. Schwedel and associates[21] also abandoned anticoagulant therapy after they started using bipolar catheters

Although the external transthoracic electrical stimulator remains a vital and necessary therapeutic adjunct for emergency situations at times pacing was not achieved with this method despite massive voltages and painful contractions of the pectoralis muscles. Moreover attacks with ventricular arrhythmias can only be controlled by continuous electrical pacing of the heart at rates which obliterate ectopic impulse formation Complications such as skin ulcerations and possible pericardial and epicardial injury[19] have also been reported. For these reasons, external pacing for more than minutes at a time is impractical. The transvenous pacemaker has proved to be ideal in these situations.

The deaths during transvenous electrical cardiac pacing were related to advanced age and associated disease Secondary failure to pace did not occur in

any. The ability to pace and improve these patients at all even though only for days, is a tribute to the method rather than a detraction.

Summary and conclusions

Short term transvenous electrical pacing of the heart was used in 78 patients 48 to 89 years of age for the relief of Stokes-Adams episodes or in the management of intractable heart failure related to a slow ventricular rate.

A unipolar catheter was used on 50 occasions, a bipolar on 46. The bipolar *catheter was found to be superior*, largely because of freedom from the need for an indifferent electrode.

The tip of the catheter was preferentially located in endocardial contact at the right ventricular apex, a position which proved to be safe. On the basis of autopsy studies, endocardial damage was shown to be absent despite such contact. On the other hand, perforations occurred twice when the tip was displaced to the outflow tract and probably occurred once when the tip was in the great cardiac vein.

Saphenous vein cutdown sites were safe and satisfactory, although jugular insertions proved to be more comfortable for the patient. The route from the arm, although feasible, was found to be potentially more hazardous. Local infection was a minor concern. Septicemia, although a major danger, was rarely encountered.

The immediate results of effective electrical cardiac pacing were usually impressive. Not only were Stokes-Adams seizures promptly and completely controlled but the mental obtundation and congestive failure, often simultaneously present, frequently cleared dramatically.

Although 26 of these patients were known to be dead at the time of this report, this eventuality was clearly a reflection of their serious disease and advanced age. The ability of this modality of treatment to improve, even transiently, these moribund individuals is a tribute to its efficacy rather than a detraction therefrom.

Short term electrical pacing of the heart is a relatively safe, effective, reliable and oftentimes lifesaving measure for the immediate control of symptomatic heart block, particularly in anticipation of implantation of a permanent pacemaker. It can also prove to be useful in the temporary management of patients with extreme sinus bradycardia, those with atrial fibrillation with slow ventricular response, and those with recurring episodes of ventricular tachycardia fibrillation unresponsive to antiarrhythmic drugs.

Transvenous pacing was successfully instituted in 40 patients after drug therapy proved to be unsatisfactory.

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A new method for recording cardiac, hepatic, and other pulsations, movements, and thrills

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Movements of the precordium are being recorded by a variety of methods and instruments although, because of technical advances and a realization of the limitations of mechanical levers and long air columns,[16] Marey and Potain's tambour levers, smoked drums and the still later Frank capsule have long since given place to crystal microphones or piezoelectric transducers and electrical multichannel recorders.

Johnston and Overy[13] and Luisada and Magri[14] reviewed the methods used until 1951 and 1952 respectively, and recently Benchimol and Dimond[4] gave a good review of the normal and abnormal apex cardiograms obtained by their method. In spite of varying methodology, the cardiac movements show a fairly comparable pattern as recorded in the precordium and the kinetocardiogram of Eddleman Harrison and their colleagues, from Alabama,[8,9,10,12,20-22] and the apex cardiograms obtained by Luisada and Magri,[16] Benchimol and Dimond[2-4] in California, or Coulshed and Epstein[7] in Liverpool are *not* much different. The "impulse record" of Belin and Mounsey[1] or what they later called "impulse cardiogram"[6,11] seems superficially to be the most different, but they were measuring the movement of the chest wall in one direction only, i.e., the direction of maximal movement, with their rigid steel rod—one knobbed end of which is pressed against the chest wall at the site of maximal pulsation—and not the total displacement of the chest wall in space, as they said.[1,5,11] It is understandable that the larger chest pieces such as that of Luisada and Magri[16] will portray displacement of one portion of the chest wall relative to the other besides the absolute precordial movements at the spot, as picked up by the 7-mm. knob of a kinetocardiograph.[9,10]

The differences in the details of the tracings are easily understandable when it is realized that the chest-piece pickup has varied in diameter from 7 mm.[8,9,10,12,20-22] to 5 cm.,[16] and that the transmission device, often an air column, has varied from a low funnel[16-17] to a column nearly a meter long,[7] which will add to the time lag in the tracing. The record pattern has also been greatly determined by the cycle frequency of the crystal microphone or the piezoelectric crystal used for conversion of changes in pressure in the air column to electrical signals and by the filter, if any, used in the recorder.[2,4,7,8,17] The position of the patient has varied from dorsal decubitus[2,16-17] to an inclination at 45 to 60 degrees,[6,11] and even to left lateral position.[2-4,7]

Even when the pickup device is placed lightly on the chest wall, it is liable to distort the movement to some degree, and

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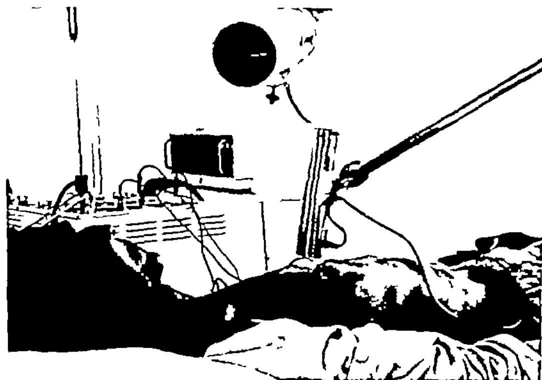


Fig. 1. The tubular photoelectric pickup device, the recorder, and the oscilloscope. The phonocardiograph microphone is not shown in the picture.

variation in its size and shape will be needed to adapt it to the chest wall, particularly *when the chest piece is large and the patient is thin with deep intercostal spaces or* has a chest deformity—congenital or acquired due to previous rickets or cardiac hypertrophy. Any attempt to make the chest piece fit closely will increase the distortion of the movement which one is attempting to record faithfully. The pressure required for close fitting, where it has been measured, was between 100 and 200 grams.[1, 11]

The present method makes use of the change in intensity of a spot of light focused on the area from which the movement is to be recorded and makes use of the photoelectric pulse pickup supplied with the three-channel Cardiopan 573* for recording the jugular venous pulse. In this, a small beam of light is thrown perpendicularly on the skin over the vein at the site of jugular pulsation and the light reflected back is collected by a ring-shaped photoelectric cell surrounding the beam of light. The beam of light is 5 mm. in diameter at the opening in the tubular pickup device, but *the spot of light is between 5 mm. and 1 cm.* broad, depending on the distance of the pickup from the skin and the angle that the beam of light makes with the surface of the skin. Except when the light is intended to be tangential for recording a thrill, the pickup with the light beam is less than 5 mm. away from the surface of the skin. An oscilloscope is connected to the Cardiopan recorder, and the angle of the beam of light to the precordium is adjusted until the monitoring oscilloscope shows the best tracing, which is then recorded along with a simultaneous ECG lead (ordinarily Lead II) and a phonocardiographic record on the same recorder but connected independently of the photoelectric pickup device. The setup of the apparatus is shown in Fig. 1. As in the case of a kinetograph, but unlike the method of Benchimol and Dimond,[2-6] an external reference frame is used here.

Recently, it has been doubted that the setup used by Benchimol and Dimond[2-6] and Coulshed and Epstein[7] is technically

*Made by F. Liechti, Ltd., Berne, Switzerland.

capable of giving a faithful record of the changes in pressure in the chest wall and an improved system of recording using an electrometer valve with the crystal microphone fitted directly to the chest piece has been described [19] Any evaluation of this system should await publication of the normal and abnormal apex cardiograms with the new suggested setup.

The present method was evolved in order to settle the disputed timing of an apical thrill (S.K. Fig 5) about a year ago, and since then excellent cardiograms in the apical region and over the tricuspid pulmonary and aortic areas have been obtained Although a large series could not be collected because recording was interrupted for some months due to a mechanical breakdown in the recorder and difficulty in replacement of parts, the results so far have been very satisfactory and are illustrated in Figs. 2 to 10 The cardiograms obtained resemble more closely the kinetocardiograms than the apex cardiograms of Benchimol and associates [2-4]

It is unjustifiable to use the term *apex cardiograms* for tracings which may be taken far away from the apex—for example, in the left parasternal area or in the pulmonary area (see Figs. 2 8 and 10) The term used here has been *cardiogram* which has been further qualified with the description of the site of the trace.

Harrison and his colleagues with their bellows-crossbar technique have demonstrated the changes in the kinetocardiogram with age [8,11] heart failure [20,21] and ischemic heart disease,[22] and the effect of exercise[21] in further increasing the prominence of the atrial wave and the mid systolic bulge and diminution or disappearance of these changes with nitrites in angina[22] and with nontoxic doses of digitalis in congestive heart failure.[20,21] Benchimol and Dimond using an entirely different apparatus that consisted of a microphone bell connected by a 5 inch long rubber tube to a crystal microphone that was attached in turn, to a multichannel electric recorder with selective filters, found a similar increase in the amplitude of the a wave in ischemic heart disease and an abnormal mid-systolic wave in their apical cardiograms.[4,5] Benchimol Dimond and their colleagues,[2-4] among others,[7,14] have shown the importance of the apex cardiogram as a reference tracing for the timing of various diastolic events and differentiation of the second heart sound from an opening snap and third heart sound for the timing of murmurs, and for help in distinguishing mitral from aortic and pulmonary di-

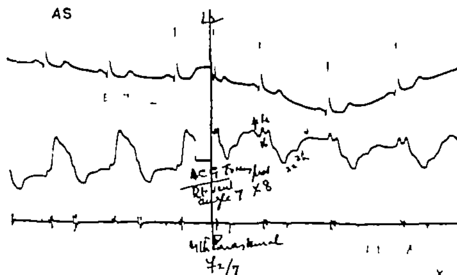


Fig. 2 A.S. Apical (*left*) and parasternal (*right*) cardiograms in 24-year-old man with moderate labile renal hypertension and slight left ventricular hypertrophy

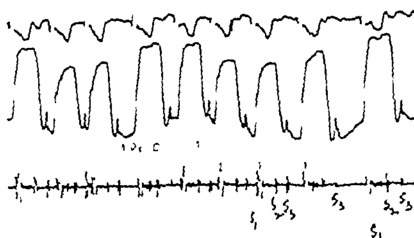


Fig. 3 G K., 18-year-old girl. Clinical diagnosis of auricular fibrillation, mitral incompetence with stenosis, and congestive cardiac failure. The apical cardiogram shows a plateau type of curve with a secondary systolic wave indicating left ventricular hypertrophy and a prominent rapid ventricular filling wave (F wave of Coulshed and Epstein) corresponding to the third heart sound. Dominant mitral incompetence.

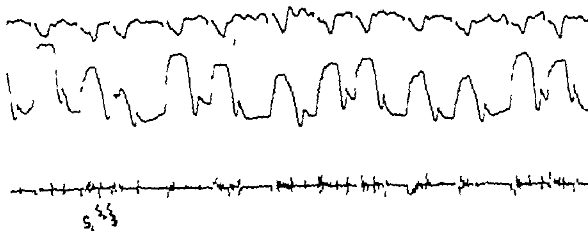


Fig. 4 Same patient as in Fig. 3. With contour light, a systolic thrill is recorded on the ascending limb of the systolic wave, better during expiration.

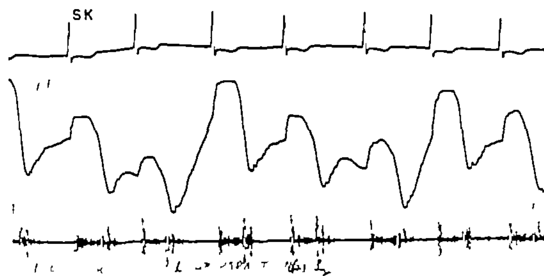


Fig 5 S K., 25-year-old woman. Clinical diagnosis of mitral stenosis with regurgitation with a massive left atrium and atrial fibrillation. *Apical cardiogram* With contour lighting a diastolic thrill is recorded particularly during expiration when the chest wall is not stretched by the inspiratory expansion. The additional sound after S_2 corresponds to the lowest point of the diastolic wave "O" and is shown to be the opening snap. Dominant mitral stenosis.

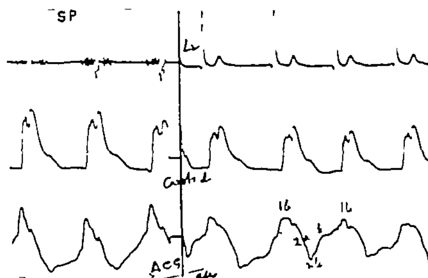


Fig 6 S P 21-year-old man. Clinical diagnosis of aortic regurgitation and stenosis. Also, mitral stenosis and mitral regurgitation. Carotid sphygmogram (*middle trace*) and apical cardiogram (*lowest trace*) A triple impact was palpated at the apex with each cardiac cycle and mid-systolic clicking sound in addition to the systolic and early diastolic murmurs, were auscultated The mid-systolic click has its counterpart in the ACG and corresponds to the nadir of the double-peaked carotid systolic ejection wave.

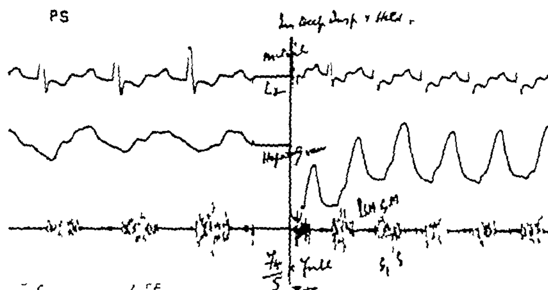


Fig. 7. P.S. 17-year-old boy. Clinical diagnosis of mitral stenosis, tricuspid incompetence, congestive heart failure, and Grade 1 A-V block. Jugular venous tracing (*left half, middle trace*) and hepatogram. The hepatogram shows that the expansile pulsation felt starts in systole and is due to tricuspid incompetence. The peak falls in early diastole. A small positive wave due to atrial systole is also seen on the ascending limb at its beginning.

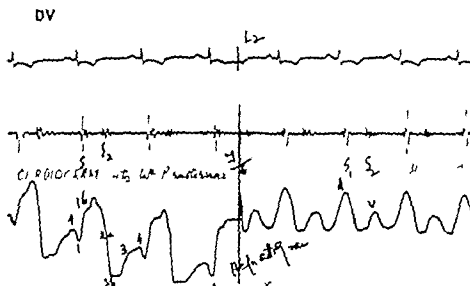


Fig. 8. D.V. 40-year-old woman. Clinical diagnosis of mitral stenosis, pulmonary hypertension with congestive cardiac failure, pulmonary incompetence, and tricuspid incompetence. Cardiogram (fourth intercostal space in the left parasternal line) (*left half of tracing*) and hepatogram (*right*). Cardiogram shows a large atrial wave and a secondary systolic wave indicating congestive heart failure and right ventricular hypertrophy. The hepatogram shows a double pulsation with the larger wave clearly due to an "a" wave secondary to pulmonary hypertension, and the second wave due to a tricuspid leak.



Fig 9 Jugular venous pulsation recorded in the same patient as in Fig 8, showing large "a" wave and a still larger combined "c and "v wave with deep "y descent due to tricuspid incompetence.

astolic murmurs, and between regurgitant and stenotic systolic murmurs.

Cardiograms are helping to put the various precordial palpatory phenomena in proper perspective and to increase the understanding of cardiac functions in health and in disease. The essential component of the heaving cardiac impulse at the apex or in the parasternal region indicative of left or right ventricular hypertrophy has been demonstrated to be the sustained character of the outward movement which is maintained up to the second sound or even beyond [8,11] The pulmonary diastolic shock in some cases of mitral valvular disease is shown to be mainly an outward systolic movement (see Fig 10) and the shock-like sensation is due to the abrupt reversal of this movement at the end of ventricular contraction and even before the beginning of the second sound A similar pattern is obtained all over the outflow tract of the right ventricle and is not limited to the site of the pulmonary artery

Apart from obtaining records indicative of left or right ventricular hypertro-

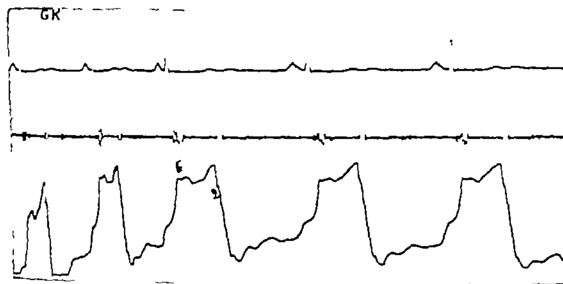


Fig. 10 G K 17-year-old girl. Clinical diagnosis of mitral stenosis with marked pulmonary hypertension Cardiogram at the site of maximal pulmonary diastolic shock in the second left intercostal space 4 cm from the midline shows it to be predominantly an outward movement during the atrial and isometric contraction phases which increases further during the later part of the ejection phase. The shock-like sensation is palpated because of abrupt reversal of this outward movement of the chest wall which starts just before the beginning of the second sound and continues steeply to the opening of the tricuspid valve and the start of ventricular filling Similar traces were obtained elsewhere over the outflow tract of the right ventricle. The first two cycles are at 25 mm. per second, and the remainder at 50 mm. per second

phy[7,8,10,11,18] (see Figs. 3 and 8) and the help one may get in the differential diagnosis of various cardiac conditions, the main value of the cardiogram lies in training the clinician to enhance his sense of palpation so as to be able to palpate and distinguish for example a third heart sound (and the corresponding movement of the chest wall) a pericardial knock or between an ejection and a mid-systolic click (see Fig. 6). Soon one begins to realize that the cardiac impulse is not simply an outward thrust due to the movement of the cardiac apex and he learns to palpate much more than only a heaving or a tapping cardiac impulse.

Thrills have been recorded with some difficulty previously.[14,15,7] It was thought that if light were focused tangentially (as in contour lighting by a photographer) it might be possible to record fine movements of the chest wall and it has been possible to record both systolic and diastolic thrills with this method (see Figs. 4 and 5) by focusing the light not as a spot but obliquely. Since the photoelectric cell records the change in the intensity of light with movement fully tangential light may cause scatter of the light outside the chest wall (which should not be interrupted by movements of bed clothes, wires, or otherwise) so that the light spot is focused obliquely and adjusted until the oscilloscope shows the thrill most clearly when it is recorded on the recorder. The advantage of this method over Levinson's[14] using a selective pulse capsule is that it gives the cardiogram and the thrill on the same trace. But it has not been possible to record every thrill that could be felt.

The simultaneous ECG, phonocardiogram and or carotid sphygmogram help to decide the timing of the various components of the tracing normal or abnormal.

It is obvious that, the larger the light spot on the chest wall the more the "relative displacement" that will be superimposed on the "absolute displacement" in the cardiogram but the basic similarity of the cardiograms obtained with chest pieces of all sizes shows that much more than due has been made of this difference. As far as the present method is concerned the slight difference is illustrated in Figs. 3 and 4 in which with contour light and a wide spot the basic pattern of the cardiogram remains unaltered and the thrill can be recorded in addition. In Fig. 6 making the light tangential and hence, widening the spot has only blunted the peak at the beginning of the ejection wave in the cardiogram (the three complexes on the right side) without changing it materially.

The same method is used to obtain epigastric and hepatic tracings. Hepatic tracings may be useful in evaluating the cause of an expansile pulsation when difficulty arises in ascertaining whether the pulsation is due to a large "a" wave in a case of pulmonary hypertension or to a superimposed functional tricuspid incompetence, or to both (see Figs. 7 and 8).

The same device can be used for recording respiratory movements, movements over an aneurysm or even a tremor or a nystagmus. Any movement which can be damped enough to be brought within the range of the recorder should be recordable by this method without any mechanical distortion of movement by the pressure of an applicator type of pickup device.

Summary

A variety of methods are being used by different workers for obtaining cardiograms at the cardiac apex and elsewhere on the precordium. All of the methods involve the use of a chest piece which is pressed against the chest wall. This pressure is liable to distort the movement of the chest wall to some degree.

A new method for picking up the movement of the chest wall with a beam of light is described and the results are illustrated with a number of tracings. The added advantage of the method is that thrills can be recorded simultaneously with the cardiograms. The same method has been used for obtaining hepatograms, and it is suggested that any tremor or rhythmic movement which can be damped enough to be brought within the range of the recorder can be recorded by this method.

The use of cardiograms in the diagnosis and investigation of heart disease has been reviewed briefly. Wider use of the cardiogram as a diagnostic aid and in the training of the physician to understand intracardiac phenomena in health and dis-

ease and in palpation of the precordium is advocated

Apex cardiogram is a misnomer for tracings which may be recorded far away from the apex of the heart These have been called *cardiograms* and may be recorded at the apex or elsewhere on the precordium

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Griseofulvin trial in angina

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Griseofulvin an antifungal antibiotic has relieved such peripheral vascular disorders as shoulder hand syndrome[1] and angiospasm of the hand associated with scleroderma[2] and dermatomyositis.[3] In the latter study an elderly patient with severe angina was noted to experience marked relief of his angina while receiving griseofulvin for the treatment of dermatomyositis. Recently DePasquale and associates[4] reported that the drug reduced the frequency of anginal attacks in 10 patients with coronary artery disease.

Some information on the pharmacologic effect of griseofulvin has been offered by the experimental study of Rubin[5] who found that griseofulvin increased coronary blood flow in vivo and relaxed isolated coronary arterial segments in vitro. The increase in blood flow was not restricted to the coronary vasculature, but occurred also in the femoral arterial bed The mechanism underlying these effects appeared to be a direct action on vascular smooth muscle rather than one mediated through the central or autonomic nervous systems It is not however certain that the coronary dilatation observed in animal experiments is in any way related to the reported anti anginal effects of griseofulvin

Materials and methods

Eight patients were selected for study All of them suffered from angina the presumptive cause of which was coronary thrombosis, and 2 of them (G.S. and R.F) had electrocardiographic evidence of myocardial infarction All patients remained ambulant during treatment and were instructed to continue their normal activities and keep other factors (e g diet smoking habits) constant in so far as possible Fine particle griseofulvin was administered in the dosage of 125 mg (1 tablet) q i.s. Exercise-tolerance electrocardiograms and fasting serum cholesterols were obtained for each patient during the pretreatment period and at the end of the 4-week and the 8-week periods of treatment. Only 3 patients (C.C R W and H M) were found to have positive electrocardiograms on exercise (Master's two-step technique) during the pretreatment period S-T depression of at least 1 mm and 0.08 second was regarded as being indicative of myocardial ischemia.

Results and discussion

The data analyzed consisted of the results from 8 patients treated with griseofulvin and placebo in random crossover The number of attacks of angina and the number of trinitrin tablets consumed per week were recorded for each patient during the 3 weeks before treatment started and during the 8 weeks of the trial The mean number of attacks and trinitrin tablets per week are shown for each patient in

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Table I *Mean number of anginal attacks per week*

Patient	*Pre-treatment*	*Drug*	*Placebo*
		weeks 1-4	*weeks 5-8*
C. C. (I)	8 00	3 75	10
G. S.	—	4 25	4 25
R. F	8 33	8 75	9 5
W C.	24 00	29 50	30 5
		weeks 5-8	*weeks 1-4*
C. C. (II)	(8 0)	9 50	16
L. M	10 33	5 50	8 50
R. W	12 33	9 25	9 50
M. J	16 33	13 50	14 75
H. M	—	—	32 0

Table II *Mean number of trinitrin tablets per week*

Patient	*Pre treatment*	*Drug*	*Placebo*
		weeks 1-4	*weeks 5-8*
C. C. (I)	10 67	1 75	15 75
G. S.	—	4 75	6 75
R. F	9 67	10 25	13 25
W C.	34 0	36 25	32 50
		weeks 5-8	*weeks 1-4*
C. C. (II)	10 67	13 00	29 75
L. M	21 67	5 00	20 75
R. W	10 00	10 00	12 75
M. J	17 67	17 50	16 50
H. M.	—	28 00	24 00

Tables I and II One patient, C C. received two courses of treatment, and his name, therefore occurs twice in each table.

Results for individual patients If it is assumed that the number of attacks per patient during each of the two 4-week periods of treatment would be about the same if griseofulvin produced no effect on angina, then Patient C C. was the only one who showed significantly fewer attacks during griseofulvin treatment than during placebo treatment. This patient showed statistically significant fewer attacks of angina while on griseofulvin during both courses of treatment. A similar effect was seen in the number of trinitrin tablets

Consideration of the number of trinitrin tablets consumed per patient shows that Patient L.M had significantly fewer tablets while on griseofulvin than on placebo and at the same time fewer anginal attacks. In none of the other patients was there a statistically significant difference between the number of attacks of angina and the amount of trinitrin consumed during griseofulvin and placebo treatment.

Over-all results The number of anginal attacks per week were recorded for only 7 of the 8 patients, whereas the number of trinitrin tablets were recorded for all patients. Table III shows the number of patients having fewer attacks of pain while on griseofulvin than on placebo 1 patient had an equal number of attacks on both treatments. Table IV shows similar results in the number of trinitrin tablets consumed The results from the second period of treat

Table III

Order of treatment	*Number of patients having fewer attacks*		*Equal number of attacks on drug and on placebo*	*Total*
	On drug	*On placebo*		
Drug-placebo	3	—	1	4
Placebo-drug	3(+1)	—	—	3(+1)
	6(+1)	—	1	7(+1)

Table IV

Order of treatment	*Number of patients consuming fewer trinitrin tablets*		*Equal number of attacks on drug and on placebo*	*Total*
	On drug	*On placebo*		
Drug-placebo	3	1	—	4
Placebo-drug	2(+1)	2	—	4(+1)
	5(+1)	3	—	8(+1)

ment of Patient C C are shown in parentheses in the tables and are not included for the purposes of assessing significance

Six of the 7 patients for whom results are available showed fewer attacks of pain while on griseofulvin than on placebo the other patient had an equal number of attacks during both periods. This is statistically significant at the 2 per cent level However 2 of the 6 patients consumed more tablets while receiving griseofulvin and this could have caused the reduction in the number of attacks in these cases.

Five of the 8 patients consumed fewer tablets while being treated with griseofulvin than while receiving placebo whereas the other 3 patients consumed more tablets while on the drug than on the placebo This difference is not large enough to be statistically significant From these results it appears that 2 of the patients showed significantly better results while receiving the drug than while on the placebo and 6 of the 7 patients for whom the number of attacks was recorded had fewer attacks while on the drug than on the placebo

No side effects from griseofulvin were found in any of the patients The administration of griseofulvin did not affect the serum cholesterol level in any patient. The positive electrocardiograms of Patients R W and H M in the pretreatment period were unchanged subsequently At the end of a 4-week period on the drug Patient W C developed a positive electrocardiogram which persisted at the end of the placebo period this might have been the result of progression in coronary atherosclerosis *in this patient In the case of* Patient C C (first course of treatment) the positive electrocardiogram became negative at the end of the drug period and then reverted to positive at the end of the placebo period. The limitations of an exercise tolerance electrocardiogram in the assessment of a drug for angina must however be realized A favorable effect on the electrocardiogram does not necessarily mean a coronary vasodilator action all that can be reasonably stated is that the drug corrects the discrepancy between the supply of oxygen to the myocardium and the myocardial demands. This may be achieved by an increase in the supply of blood to the heart a reduction in the myocardial consumption of oxygen an increase in the efficiency of the heart or any combination of these different aspects [6]

Summary

Eight patients were selected for a double-blind griseofulvin trial in angina Two of the patients showed significantly better results while receiving the drug than while on the placebo and 6 of the 7 patients for whom the number of attacks was recorded had fewer attacks while on the drug than on the placebo No side effects from the drug were found in any of the patients. Serum cholesterol was unaffected by the drug and a favorable effect on the post exercise electrocardiogram during the drug period was observed in only 1 of the 3 patients in whom the pretreatment electrocardiogram was positive on exercise

One could not really expect conclusive results from such a small number of patients but these results may well justify the carrying out of further work on this subject

We are grateful to Dr M Anderson Consultant Physician Ingham Infirmary South Shields, England for allowing us to undertake this trial to Mrs. Wilson for secretarial assistance and to Dr R H E. Grant Division Medical Department, I C I Ltd for supplying the drug and placebo, and for statistical analysis of the results.

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Electrocardiographic changes in gastric freezing

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Gastric freezing has been reported since 1958 as a form of treatment for peptic ulcer or hiatal hernia.[1-4] Considerable experience has been gained with this new type of treatment, although at the present time there is no general agreement as to its usefulness.

Several electrocardiographic abnormalities have been reported during gastric freezing.[5-7] The purpose of this paper is to describe and evaluate the electrocardiographic changes in patients who have undergone such procedures.

Material and methods

Sixty-four patients with peptic ulcer and/or hiatal hernia that was corroborated by upper gastrointestinal series underwent gastric freezing. In one case the procedure was repeated after 4½ months, making a total of 65 studies. Only 1 of the 64 patients had arteriosclerotic heart disease; the rest had no prior symptoms or signs of heart disease. Fifty-six were men and 8 were women. Their ages ranged from 19 to 63 years, with an average of 39.8 years. Duodenal ulcer was the reason for gastric freezing in 51 patients, hiatal hernia in 5, a combination of both in 7, and marginal ulcer in 2. Freezing was performed with a low temperature gastric hypothermia machine. Absolute ethyl alcohol was circulated into a stomach-shaped balloon by means of a double-lumen tube. In-going temperatures were −15 to −19 degrees, and out-coming temperatures were −7 to −10 degrees centigrade. Perfusion time ranged from 55 to 70 minutes.

Fifty-four patients had a normal control electrocardiogram. Among the other 10 patients, there was a low voltage in 1, possible left ventricular hypertrophy in 4, questionable right ventricular hypertrophy in 2, incomplete left bundle branch block in 1, incomplete right bundle branch block in 1, and probable electrolytic disturbance with auricular extrasystoles in 1. Diffuse changes in subepicardial ventricular repolarization were present in the patient with arteriosclerotic heart disease. In 55 instances, three traces were taken: one as a control, another during the period of

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Table I. Variations and average values of heart rate A_{QRS}, A_T, and Q-T MV before, during and after gastric freezing

Freezing	Heart rate	A_{QRS} (degrees)	A_T (degrees)	Q-T MV (sec./100)
Before	45 to 115 75	−50 to 130 50	0 to 70 40	−5 to 11 1
During	50 to 145 86	−60 to 130 43	−40 to 60 −3	−2 to 11 4
After	40 to 110 74	−60 to 120 50	−40 to 70 38	−5 to 10 1

perfusion and the third 90 minutes after the procedure had been completed. In 5 cases six tracings were taken: one prior to freezing, another during it, and the other 4 at 15 minute intervals after completion of the procedure. In the last 5 cases, prefreezing and transfreezing electrocardiograms were also taken and postfreezing electrocardiograms were recorded at the rate of one every 5 minutes until the tracing became normal.

Results

Rhythm. Normal sinus rhythm was always preserved except in the patient with coronary insufficiency, in which case coronary sinus rhythm appeared during the perfusion time and remained throughout the postfreezing tracing.

Extrasystoles. These were registered in 5 patients (7.7 per cent) during freezing. In 4 of these patients the extrasystoles were supraventricular, one of them having a short run of paroxysmal tachycardia. The other patient presented occasional right ventricular extrasystoles. Supraventricular extrasystoles disappeared in the postfreezing tracing, in contrast to ventricular extrasystoles, which persisted and even increased. The auricular extrasystoles that were registered in the control electrocardiogram of one patient disappeared during gastric freezing. Another patient registered sinus arrhythmia with bradycardia during freezing, which increased at the end of the procedure.

Heart rate. The heart rate *increased* in 48 (73.8 per cent) from 5 to 65 beats per minute with an average of 24 beats. It *decreased* in 14 cases (21.6 per cent) from 5 to 50 beats per minute, with an average of 13 beats and remained *without change* in 3 cases (4.6 per cent).

A_{QRS}. A_{QRS} developed a shift to the *left* in 39 cases (60 per cent) from 5 to 60 degrees, with an average of 18 degrees. It rotated to the *right* in 10 cases (15.4 per cent) from 5 to 20 degrees, with an average of 13 degrees, and remained the *same* in 16 cases (24.6 per cent).

A_T. A_T rotated to the *left* in 62 cases (95.4 per cent) from 5 to 100 degrees, with an average of 43 degrees. There was no deviation to the *right* in any case. It remained the *same* in 3 cases (4.6 per cent).

*Q-T MV.** Q-T MV *increased* in 54 cases (83 per cent) from 0.01 to 0.09 second with an average of 0.03 second. It *decreased* in 2 cases (3 per cent) 0.01 second in both and remained the *same* in 9 cases (13.8 per cent) (Table I).

Wave abnormalities. The T wave decreased its voltage, becoming negative or increasing its previous negativity in Leads D_{II}, D_{III}, and VF in 95.4 per cent of the cases. The QRS underwent slight changes in voltage in peripheral leads in connection with the A_{QRS} changes. The P wave, P-R interval, and S-T segment did not show meaningful changes (Figs. 1 and 2).

All previous changes described disappeared within the first 5 to 15 minutes after cessation of freezing except in the patient with arteriosclerotic heart disease in whom coronary sinus rhythm appeared and posterolateral subepicardial ischemia had a slight increase. No patient complained of anginal pain during gastric freezing.

*Values of the Q-T interval in relationship to the Mean Value, in accordance with Bazett formula: $Q\text{-}T = 0.39\sqrt{R-R}$.

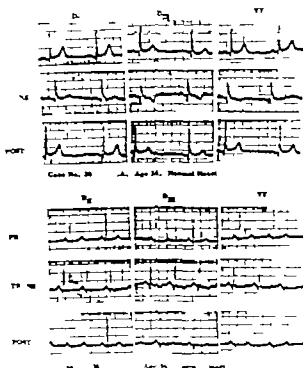


Fig. 1 Electrocardiograms taken before, during and after freezing. Notice the alteration of the T wave during the procedure and its normalization after completion of freezing.

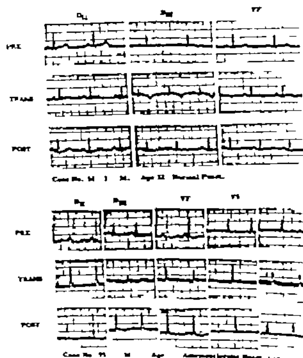


Fig. 2 Case 51. Similar to that seen in Fig. 1 is alteration of the T w during freezing with recovery after the procedure. Case 55. Changes in the T wave are not so marked as in the patients with a normal heart. However the pre-existing abnormality of the T wave increased in the tracing after freezing.

Discussion

Distention and freezing of the stomach for 1 hour caused the following electrocardiographic changes listed according to incidence (a) decrease in voltage, inversion or increase of pre-existing negativity of T wave in Leads D_{II} D_{III} and VF with the consequent rotation of A_T to the left (b) increase in electrical systole (Q T interval) (c) sinus tachycardia (d) *rotation of A_{QRS} to the left and* (e) temporary extrasystoles

Among these changes the most important was that demonstrated by the T wave on the diaphragmatic side of the heart Several hypothesis may be postulated to explain this fact (1) Alanis and Mascher [4] in experiments with dogs showed that the sustained distention of the gastric walls by *an inflated rubber balloon in the* stomach resulted in a decrease in coronary output of approximately 10 to 12 per cent along with an increase in efferent impulses of the sympathetic heart nerves. This occurs through the mechanical stimulation of the gastric tension receptors which send afferent impulses that are conducted by the vagus and splanchnic nerves (2) The *gastric chemoreceptors are stimulated by* freezing and coronary vasoconstriction is produced by sympathetic reflex (3) Horizontalization of the heart occurs because of displacement by the stomach (4) The subepicardial region of the left ventricle is cooled which alters its repolarization

The first two hypothesis, which explain T wave changes by coronary vasoconstriction *decrease in coronary output* and ischemia would not explain why such alteration is only posteroinferior instead of being diffuse as is to be expected

The third hypothesis, horizontal position of the heart displaced by the distended stomach could in fact contribute in some extent *to the rotation of A_T to the left* with the consequent alterations of the T wave in peripheral leads. However we believe that this explanation is not satisfactory either since we did not find a shift to the left of A_P and A_{QRS} proportionate to that of A_T as would be expected with a change in the position of the heart Furthermore Wilson and Finch[9] reported that T wave changes caused by ingestion of 600 c.c of cold water were not present when the same amount of hot lemonade was given

The fourth hypothesis appears to be the most likely explanation of the alteration of the T waves. The fundus of the distended stomach makes contact with the posterior inferior region of the left ventricle as was demonstrated radiologically by Wilson and Finch[9] in *1923* These authors stated that the cooling of the stom*ach is transmitted to the closer superficial* areas of the myocardium which in turn delay their repolarization Since subendocardial areas are not affected in the same manner by cooling [10] recovery takes place first in these regions with the consequent inversion of the repolarization process, which is then from endocardium to epicardium Thus, with the negativity of the *repolarization vectors in front* the epicardial electrodes will register negative T waves in those leads facing the diaphragmatic aspect of the heart [11]

As for the other changes produced in the electrocardiogram by gastric freezing the increase in electrical systole (Q-T interval) would also be due to the retardation of metabolic processes in the myocardium *produced by cooling with the subsequent* delay in ventricular repolarization Tachycardia may be explained by the already mentioned sympathetic reflex stimulation and probably by the increase in circulating catecholamines due to the stress caused by the freezing procedure. This same factor *could account for the augmented auto*matism of the heart with the production of extrasystoles.

Summary and conclusions

A study was made of the electrocardiograms of 65 patients with peptic ulcer and/or hiatal hernia treated by gastric freezing

Freezing was performed by perfusing absolute ethyl alcohol into a gastric balloon for 55 to 70 minutes. Inflow temperatures were −15 to −19°C and outflow temperatures were −7 to −10°C

Electrocardiograms were recorded before during and after freezing The most frequent changes were a decrease in voltage *or inversion of the T wave in Leads D_{II}* D_{III} and VF prolongation of the electrical systole, and tachycardia Left deviation of A_{QRS} and extrasystoles were observed

with lower incidence These alterations disappeared slowly within the first minutes after completion of the freezing except in one patient who previously had arteriosclerotic heart disease

The possible explanations for these changes are discussed

Addendum

Since completion of this report gastric freezing has been performed on another patient who had an old myocardial infarction No electrocardiographic changes were observed during or after freezing

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The relative significance of high-frequency and low-frequency notching in the electrocardiogram

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It has been shown that the finding of an abnormal number of high-frequency notches and slurs in the QRS complex of the high-fidelity electrocardiogram made with an expanded time scale and a wide band recorder is a valuable adjunct in the evaluation of coronary heart disease.[1-4] In this study, the total number of high frequency notches and slurs in several combinations of leads was examined in order to determine which combination provided the best separation between normal and abnormal subjects. It was found that the sum of the number of high-frequency notches and slurs in the six precordial V leads plus those in the three largest limb leads was most meaningful. In addition, for each subject, the total number of low frequency notches in the nine above-mentioned leads was counted from the conventional electrocardiograms taken at the same time as the high frequency electrocardiograms. Previous investigators found that the low frequency notches have diagnostic significance.[5-7] However, as will be shown in this paper, high-frequency notching is more prevalent and provides more diagnostic information than low frequency notching when records are made with a high-fidelity system.

Methods and material

The method used for recording the high-fidelity high frequency electrocardiograms has been reported elsewhere.[1,3] In summary, this method employs three features: (1) a recording system with a wide frequency band (0.1 to over 1,000 cycles per second); (2) an expanded time scale twelve to fifteen times faster than that of conventional electrocardiography; and (3) a high gain per millivolt, so that when the QRS is displayed on a cathode-ray oscillograph, the amplitude is 50 to 100 millimeters per millivolt, depending on the voltage of the signal being recorded. A routine low frequency electrocardiogram on a conventional direct writing Sanborn Viso-Cardiette was also recorded at the same time that the high-fidelity electrocardiogram was made.

The high-fidelity records used in this study were made by photographing the trace of the cathode-ray oscilloscope with a high-speed photographic paper transport. The paper speed was approximately

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380 millimeters per second in Figs. 1, 2, and 5. The paper speed was approximately 350 millimeters per second in Figs. 3 and 4. There are time and amplitude scale markings on the conventional electrocardiograms which are mounted with the same lead recorded simultaneously by the high fidelity technique. Mounted at the top of Figs. 2 and 5 are records of oscillations with a frequency of 100 cycles per second in order to provide a time scale. The time scale oscillations are routinely recorded simultaneously with the electrocardiogram on a second channel of the oscilloscope.

The differentiation between high frequency and low frequency notches and slurs was determined as a matter of expediency in the following manner. The frequency response of the direct writing instrument with which most of our conventional electrocardiograms were made was satisfactory to an upper limit of approximately 80 cycles per second, and the paper speed was the usual 25 millimeters per second. Notches and slurs revealed by this system of recording were classified as low frequency. When these same notches were seen in a much expanded form on the high-fidelity tracing, they were not included in the high-frequency count. However, *all* additional notches and slurs were counted as high-frequency components. From previous studies using high-pass and low-pass filters with variable band widths, it had been determined that most high-frequency notches require an instrument that has a frequency response which is substantially flat between 200 and 500 cycles per second.[10] The high fidelity equipment that we used had a frequency response flat from 0.1 to 1,000 cycles per second. Although this gave better definition and sharper notches in records having small high-frequency components, reduction of the upper limit of the band width from 1,000 to 500 cycles per second does not obliterate the very fast notches and slurs.

The same limb and precordial V lead positions were used for both the conventional and the high-fidelity *technique*. The six limb leads were aV_L, I, aV_R, II, aV_F, and III. Either the lead of smallest absolute amplitude or the lead with an equiphasic QRS having a net algebraic area approximating zero was designated as the smallest lead for the purpose of analysis. The lead perpendicular to such a small lead in the hexaxial reference system was called the largest limb lead. Additional precordial V leads were made at least one intercostal space above and below the site of any regular V lead which showed notching. In high-frequency records, special care must be taken to avoid skin and muscle noise and electrical interference, particularly the harmonics of 60-cycle current. The precautions to avoid artifacts have been covered in previous publications.[7,8]

The abnormal subjects used in this study were 100 men 43 to 75 years old (mean age of 56 years) who were fully ambulatory after surviving a well-documented episode of myocardial infarction diagnosed by a well-qualified cardiologist on the basis of typical symptoms, electrocardiographic changes, and other confirmatory laboratory studies. The tracings used for this study had been made from 5 to 10 years ago. As a control, records from 100 subjects were used which had been taken 8 to 12 years ago, so that a control group could be selected in which no person had subsequently had any clinical evidence of coronary heart disease for at least 8 years after the control electrocardiogram. At the time the records for the control group were taken, the ages of the subjects ranged from 38 to 67 years (average of 51 years). These control subjects were followed by yearly health examination which consisted of comprehensive physical examinations that included postexercise electrocardiograms and studies of blood lipids.

As in a previous study,[11] simple mathematical curves were fitted to the data on high frequency notches in order to smooth out random fluctuations and also to provide a means of estimating the probability that a normal subject would have more than thirteen high frequency notches or that an abnormal subject would have less than seven high frequency notches in the nine leads studied.* In the case of both the normal and the abnormal groups the curve

*These nine leads are the six precordial V leads plus the three largest limb leads. Whenever the term "notches" is used it is also meant to include short, bending or any other similar brief abrupt change in smooth QRS, except the normal peaks and nadirs of the QRS.

was fitted in two parts. Straight lines were fitted to the data for six notches or less for the normal group and for fifteen notches or less for the abnormal group Exponential curves of the type $Y = AB$ were fitted to the data for seven or more notches for the normal group and for sixteen or more notches for the abnormal group The curves were fitted by the method of moments, and when tested by the chi-square (X^2) test, the curves appear to fit the data very closely

Results

In the presentation of the results, typical examples of records illustrating both high frequency and low frequency notching and slurring will be shown first Such records, with the exception of Fig 5 form the basis of the statistical tables. Next, the results of a mathematical analysis of the probable significance of the numbers of notches and slurs in three single leads and two lead combinations will be described and presented in tabular form and finally clinical follow up information about the normal and abnormal groups will be summarized

Fig 1 is a normal two-channel high fidelity record of V and V without notching or slurring

Fig 2 shows marked notching or slurring in the high frequency record of V, whereas the low frequency electrocardiogram has no definite notching or slurring

Fig 3 shows well-defined excessive high frequency notching but only one barely perceptible notch in Lead II and no notch or slur in V_4 of the conventional low frequency electrocardiogram in the same subject

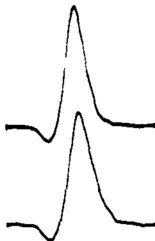


Fig 1 Shows the QRS of V and V recorded by the high-fidelity technique. *The wave form is smooth, without significant notching or slurring*

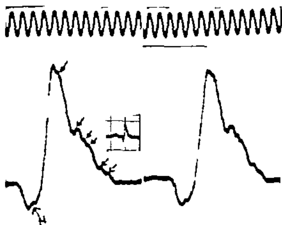


Fig 2 Shows two consecutive QRS complexes recorded by the high fidelity technique from the V position and one simultaneously recorded QRS from V of the same subject, recorded with the conventional direct writing electrocardiograph Four notches and two slurs appear in the high fidelity tracing but these fast components are obscured the conventional record The high-frequency time base, 100 oscillations per second of the second QRS *was removed from the extreme top of the 5-inch* recording paper and placed directly above the QRS



Fig 3 Limb Lead II on the left and V on the right, showing high-fidelity and conventional records from the same subject. Both lead reveal several notches and slurs in the high-fidelity record but only one barely perceptible notch in Lead II of the conventional record.

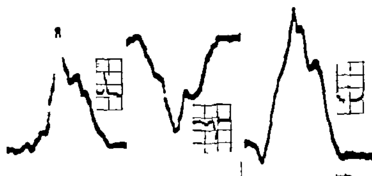


Fig 4 Shows the three largest limb leads, I aVR and II in the same subject. High fidelity and conventional electrocardiograms were recorded at the same time In the latter there is excessive low frequency notching and slurring In the high-fidelity electrocardiogram there is an excess of both high-frequency and low-frequency notching and slurring

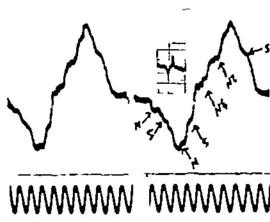


Fig 5 Biphasic Lead aVF with a deep Q wave. Two consecutive QR complexes are shown for the high-frequency electrocardiogram revealing marked notching and slurring as identified by the letters N and S on the record. The simultaneously recorded conventional electrocardiogram shows only one thick slur The high-frequency time base was moved from the top of the original recording for compactness, as explained in the legend of Fig 2.

Fig 4 shows marked notching in the high frequency range and also excessive low frequency notching in the same leads, as revealed by the conventional electrocardiogram

Fig. 5 shows the type of biphasic lead not counted as a large limb lead yet this particular lead is of diagnostic significance. When the high fidelity electrocardiogram was employed and high-frequency notching and slurring were used as the sole criteria, the total number of notches in nine leads, that is, the three largest limb leads and the six precordial V leads, provided the best statistical separation between normal controls and coronary cases. However in twelve abnormal subjects, diagnostic Q waves in aVF and III caused these leads to show relatively biphasic QR complexes. The net algebraic area of Q plus R was small so that the lead was placed in the category of relatively small leads, and its notching therefore was not included in the total number of notches in the three limb leads of largest amplitude used in the statistical analysis. Such biphasic limb leads containing diagnostic Q waves frequently revealed the presence of marked notching which supported the diagnosis of infarction and often revealed myocardial damage beyond the Q wave. An example of such a multinotched QR complex is shown in Fig 5 The large number of notches in Fig 5 is twice the largest number of notches observed in a single small limb lead of any normal control

In studying the electrocardiograms of our 200 subjects, we found by the method of trial and error that the best gross separation between abnormal and normal subjects was obtained by using the total high-frequency notches in a combination of nine leads consisting of the six precordial leads and the three large limb leads. This combination of leads was then analyzed mathematically as previously described in the section on methods.

Table I shows the distribution of the

Table I. Combined total of high frequency notches and slurs in six precordial leads and three largest limb leads

Number of components	*Number of abnormal subjects*	*Number of normal subjects*
0	0	10
1	0	12
2	0	8
3	0	12
4	0	9
5	0	7
6	0	12
7	2	10
8	3	7
9	2	4
10	5	2
11	6	1
12	2	1
13	5	5
14	10	
15–16	18	
17–19	19	
20–24	16	
25–29	9	
30–33	3	

persons studied according to the number of high frequency notches and slurs observed in the nine leads studied. Seventy-five of the abnormal group had fourteen or more high frequency components whereas none of the normal group had over thirteen such components. There was an overlap of the groups having seven to thirteen notches and slurs, in that this encompassed 30 normal and 25 abnormal subjects. All of the other 70 members of the normal group had less than seven high frequency notches and slurs in the nine leads. However, none of the abnormal group fell in this low numbered category.

Table II shows for each group the probability that an individual would show a given total number of high frequency notches and slurs. The probabilities in Table II are based on the fitted curves which were described in the section on methods.

Table III shows the probability that a person with a given total number of high-frequency notches and slurs has coronary heart disease. For instance, Table III shows that there is an 81 per cent probability that a person with a total of sixteen notches has coronary heart disease in

Table II. Probability of having a given total number of high frequency notches and slurs in six precordial leads and three largest limb leads

Number of component	*Abnormal*	*Normal*
6 or Less	0036	7029
7	0126	1004
8	0216	0665
9	0306	0440
10	0395	0291
11	0485	0193
12	0575	0128
13	0664	0084
14	0754	0056
15	0844	0037
16	0971	0025
17	0803	0016
18	0663	0011
19	0548	0007
20 or More	2614	0014

Table III. Probability that a person with a given total number of high frequency notches and slurs in six precordial leads and three largest limb leads falls into the abnormal class*

Number of component	*Probability*
6 or Less	Less than 005
7	01
8	04
9	07
10	13
11	22
12	34
13	46
14	60
15	72
16	81
17	85
18	87
19	90
20 or More	95

other words, his chances of having coronary heart disease are four to one. This table is based on two assumptions. The first assumption which was also made in the report of the previous study is that 10 per cent of the total male population in the age range studied has manifest coronary heart disease. The second assumption is that no information is known except the total number of notches for the nine leads. This second assumption is a hypothetical situation, since there would usually be additional clinical evidence of considerable diagnostic significance available in any particular case. With due regard to these assumptions, Table III indicates that a person who has more than thirteen high-frequency notches and/or slurs for the nine leads is very likely to have coronary heart disease.

In a previous paper it was reported that there is a high probability that a given subject has coronary heart disease when there are more than two high frequency notches in the QRS complex of either Leads V_5, V_6, or the largest limb lead and also when the sum of the notches in V_5 and V_6 plus those of the largest limb lead totals more than four.[9] Thus far we have suggested five different tests based on high frequency components to determine whether an individual has coronary heart disease. The question naturally arises as to which test is the most effective. A measure of this is afforded by Tables IV and V which are based on the same assumptions as Table III.

Table IV was an intermediate step in the derivation of Table III. It shows for a hypothetical random sample of 1,000 males in the age range studied the expected number of them in the abnormal and normal classes with a given total number of high frequency notches and slurs for the nine leads. Table V is based on Table IV and the corresponding tables in the report of the previous study[11] and shows how many people out of a thousand would be correctly or incorrectly classified if certain rules were used. Table V also shows how many of the hundred people with coronary heart disease expected in a random sample of a thousand would be correctly classified by the same rules. It seems to be reasonable to conclude that a test based on the nine leads combined and using twelve or thirteen notches or slurs as the critical number is more precise than any of the other criteria used because it detects a high proportion of persons with coronary heart disease while incorrectly classifying the least number of people.

Table IV. Expected distribution of 1,000 people according to total number of high frequency notches and slurs in six precordial leads and three largest limb leads

Number of components	*Abnormal*	*Normal*
6 or Less	0.4	632.6
7	1.3	90.4
8	2.2	59.8
9	3.1	39.6
10	4.0	26.2
11	4.8	17.4
12	5.8	11.5
13	6.6	7.6
14	7.5	5.0
15	8.4	3.3
16	9.7	2.3
17	8.0	1.4
18	6.6	1.0
19	5.5	0.6
20 or More	26.1	1.3
Total	100.0	900.0

Table VI shows the combined number of *low*-frequency notches and slurs observed in the six precordial leads and the three largest limb leads of the conventional electrocardiogram. It can be seen at a glance that no normal subject had more than four low frequency notches, and only 10 out of 100 had more than two whereas among the abnormal subjects, 54 out of 100 had more than two notches. Tables for low frequency notching corresponding to Tables II through V for high frequency notching were not prepared for this data because the only mathematical curve which gave a reasonable fit to the data for the normal group indicated that it is impossible for a member of the normal group to have more than four low frequency notches for the nine leads, and we were unwilling to draw such an extreme con-

Table V. Number of people out of 1,000 who would be correctly and incorrectly classified if all persons with more than the critical number of high-frequency components in the leads listed in Column 1 were classified in the abnormal group and all other persons were classified in the normal group

Leads	*Critical number of high-frequency notches and slurs*	*Number* correctly classified as abnormal*	*Normal subjects incorrectly classified as abnormal*	*Abnormal subjects incorrectly classified as normal*	*Total incorrectly classified*
(1)	*(2)*	*(3)*	*(4)*	*(5)*	*(6)*
V_4	1	43.8	21.5	56.2	77.7
	2	24.8	3.3	75.2	78.5
V	1	37.4	8.2	62.6	70.8
	2	19.4	.8	80.6	81.4
Largest limb lead	2	32.5	25.7	67.5	93.2
Three leads combined	3	56.3	18.5	43.7	62.2
(V_4, V_5, and largest limb lead)	4	45.8	7.0	54.2	61.2
	5	35.9	2.6	64.1	66.7
Nine leads combined	11	84.2	34.0	15.8	49.8
(six precordial leads and	12	78.4	22.5	21.6	44.1
three largest limb leads)	13	71.8	14.9	28.2	43.1
	14	64.3	9.9	35.7	45.6
	15	53.9	6.6	44.1	50.7

*In a hypothetical sample of 1,000 persons, it is expected that there would be 100 persons with coronary heart disease and 900 normal subjects. Therefore, the numbers in Column 3 also represent the percentage of persons with coronary heart disease who would be detected by the particular test.

Table VI. Combined total of low-frequency notches and slurs in six precordial leads and three largest limb leads for conventional electrocardiogram

Number of components	*Number of abnormal subjects*	*Number of normal subjects*
0	12	41
1	18	28
2	16	21
3	20	7
4	22	3
5	7	
6	2	
7	1	
8	1	
9	1	

clusion on the basis of a hundred people. However, it does seem to be reasonable to assume that the probability of such an occurrence is very low and, as a corollary, it is very likely that a person with more than four low-frequency notches for the nine leads studied has coronary heart disease.

Information about the subsequent course of the two groups studied will be presented next as a very brief summary. All members of the control group are still in good health with the exception of 6 subjects who have recently developed myocardial infarction 8 to 12 years after the control records were made but who have made excellent recoveries and, in 5 instances, returned to work. The only death in our control group was due to a noncardiac disease. In the original records studied which were made 8 to 12 years ago on the control group the number of notches was very small as compared to the number in the

abnormal group as can be seen in Table I. Among 20 postinfarction subjects in whom the conventional electrocardiogram had returned to normal, 15 had a total of fourteen or more high-frequency notches or slurs in the nine leads recorded with the high-fidelity technique. Eighty postinfarction subjects had residual inverted T waves and/or abnormal Q waves. Of these, 60 had fourteen or more high-frequency notches in the nine leads studied. A follow up of the postinfarction subjects was made, but only 51 subjects could be traced. Thirty-seven subjects were dead, and the cause of death in 34 was given as heart disease. In the 34 who died of heart disease, 32 had over fourteen high frequency notches, and *in 18 of these cases* there were twenty or more high-frequency notches in the nine leads studied. Although this material is too incomplete for statistical analysis, there is a trend which suggests that the higher the number of notches, the graver the prognosis.

Discussion

Low frequency notching is mentioned in some textbooks on electrocardiography and several investigators have evaluated its significance.[1-7] However, in recent years, low frequency notching has been relegated to a minor or even inconsequential role by most electrocardiographers. In fact, the latest edition of the Medical Impairment Bureau code book,[17] which is used by all the leading life insurance companies, does not provide a code symbol for notching of the electrocardiogram. One important cause for the loss of interest in low frequency notching is the fact that, even in the best recorded direct writer electrocardiogram, notching is unimpressive or even completely obscured when the usual paper speed of 25 millimeters per second is used, whereas the same electrocardiographic lead recorded with high-fidelity equipment shows obvious low frequency notching. In our conventional electrocardiograms it was necessary to use a two-power magnifying glass to find most of the low frequency notching reported here. Records made by the high fidelity technique reveal high-frequency notches and slurs obscured in conventional records. Even low frequency notches can be identified with much greater ease and assurance.

In our experience the high fidelity technique has been a valuable adjunct in the evaluation of coronary heart disease for the following reasons. One reason is the results reported in this paper on the relationship between the number of notches and slurs and the probability of coronary heart disease. In addition, high fidelity electrocardiograms have shown notching as a serial change in the QRS preceding a full-blown myocardial infarct before any other diagnostic changes appeared in the conventional electrocardiogram. In borderline conventional electrocardiograms, excess notching of the QRS in high-fidelity records has indicated the presence of myocardial damage, and this was proved to be a valid finding as shown by the subsequent course of the case.[4]

In the presence of diagnostic Q-wave or T wave abnormalities, excess notching of the R wave in the QR complex or of the R wave in other leads indicates myocardial damage beyond the Q wave. The validity of this last statement is supported by the experimental work of Durrer and his colleagues.[12,13] The latest work of Durrer[13] reveals that this degree of more extensive myocardial damage is not revealed in the conventional electrocardiogram.

It is of interest that each of the 12 members of the abnormal group reported here who had more than four low frequency notches also had more than fourteen high-frequency notches, and 7 of them had more than twenty-one high-frequency notches. This indicates that, in so far as high-frequency and low frequency notching are concerned, the use of high-frequency notching alone is adequate for diagnosis. Although the high-frequency electrocardiogram provides a significant increase in information as compared to the conventional electrocardiogram, it can be seen that notching of multiple leads is significant for any electrocardiogram.

Summary

The number of high frequency notches and slurs and the number of low frequency notches and slurs were compared in two groups of individuals. One group consisted of 100 normal control subjects. The second

group consisted of 100 ambulatory subjects who had recovered from an acute myocardial infarction. In the latter group, the conventional electrocardiogram of 20 subjects returned to normal after they had recovered from their infarctions. However in 15 of these 20 subjects the high frequency electrocardiogram still showed an abnormal number of notches and slurs. A mathematical analysis based on the theory of probability was made of the number of notches and slurs for both normal and abnormal groups. It was found that the sum total of notches and slurs in the six precordial V leads plus those in the three largest limb leads was the best criterion based on high frequency components to distinguish between the normal and abnormal groups Although low frequency notching was more prevalent in persons with coronary heart disease than in normal control subjects, it was less prevalent and less informative than high frequency notching in abnormal subjects. Evidence has been presented which lends further support for the value of the high frequency notching and slurring found in the high fidelity electrocardiogram as an adjunct in evaluating coronary heart disease

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Anticoagulants in acute myocardial infarction

The failure of anticoagulants to alter mortality in a randomized series

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The effectiveness of anticoagulation in decreasing mortality in acute myocardial infarction was seemingly established by the early studies of Wright and his colleagues.[1-3] For the following several years, such therapy was almost universally accepted.[4] More recently, however, following the report of Hilden, Iversen, Raaschou and Schwartz,[5] which indicated no benefit from anticoagulation, others have expressed serious doubts about the value of a difficult, troublesome and potentially dangerous regimen.[6] Russek and his associates have taken an intermediate position by advocating anticoagulation for only those patients who fail to qualify as "good risks" upon application of those authors' specific criteria.

To further elucidate the efficacy of anticoagulant therapy in acute myocardial infarction, we have randomly assigned 147 consecutive patients with recent myocardial infarction to treatment regimens differing only in the use or avoidance of oral administration of warfarin. Mortality and complications in the anticoagulated and nonanticoagulated groups were compared.

Methods and materials

This study was conducted on the cardiovascular ward of the Veterans Administration Hospital, Richmond, Virginia, from March, 1960 through June, 1963. All of the male patients admitted to that ward with a diagnosis of acute myocardial infarction which had occurred within 1 week prior to admission were included in the

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study. The diagnosis of myocardial infarction was accepted only when all three of the following criteria were met (1) chest pain suggestive of coronary disease (2) electrocardiographic changes of infarction (pathologic Q wave) or serial alterations in the S-T segment and T wave (3) elevation of the serum glutamic oxaloacetic transaminase above 40 units if the patient survived 3 days. Since all patients were admitted to the same ward they were treated by the same group of physicians and nurses. Care other than anticoagulation varied little. One hundred and forty seven patients who met the above mentioned criteria comprised this study.

The 147 patients were divided into two groups. Those patients who had been assigned even hospital unit numbers received anticoagulants, and those with odd numbers did not. The hospital unit numbers were assigned in consecutive order by a clerk to all patients, regardless of presenting complaint who appeared at the hospital admitting room. The clerk was completely unaware of this study. The treated group was further divided according to the level of anticoagulation. The group designated as adequately treated had Quick one-stage prothrombin concentrations between 10 and 30 per cent for 75 per cent of the time after the first 2 days that followed the onset of anticoagulant therapy. Those not meeting such criteria have been designated as inadequately anticoagulated. The 147 patients may thus be divided into 70 patients who received no anticoagulants, 46 in whom therapy was considered to be adequate and 31 who were considered to be inadequately treated. These proportions are in keeping with those reported in the literature.

The anticoagulant used throughout the study was warfarin sodium. No patients were treated with heparin alone but 33 of the 77 of the treated group received heparin for the first 48 hours.

Table I. Incidence of factors affecting mortality in the groups with various grades of anticoagulant therapy

Factors	No anticoagulation	Anticoagulation	Adequate anticoagulation	Inadequate anticoagulation
Number of patients	70	77	46	31
Age—Mean (Range)	58 (34–75)	57 (35–73)	60 (35–73)	53 (37–73)
Weight (pounds)—Mean	161	161		
History of hypertension	19%	26%	26%	26%
History of valvular heart disease	0	1	0	3
History of cerebrovascular accident	3	8	6	10
History of diabetes mellitus	9	14	11	20
History of arteriosclerosis obliterans	7	8	4	13
History of congestive heart failure	40	18	15	23
Duration of heart failure				
Less than 1 mo.	9	1	0	4
1–12 mo.	15	7	9	4
More than 12 mo.	13	3	2	4
Family history of arteriosclerosis	39	30	28	32
Previous myocardial infarction	23	18	22	13
Collapse	7	8	6	10
Cardiomegaly	24	13	15	10
Acute pulmonary edema	9	5	9	0
Shock	13	17	13	16
Congestive heart failure	37	30	30	29
Digitalis	27	26	28	23
Quinidine	13	17	20	13
Pronestyl	6	3	4	0
VPCs greater than 1/10	20	14	13	16
VPCs greater than 1/5	10	11	13	7

The data for this study were obtained by reviewing each patient's hospital chart and recording the data on a printed form containing 64 questions pertaining to the patient's history, physical findings and hospital course. This information was placed on IBM punch cards and on punched paper tape. An RPC 4000 digital computer was used to perform chi-square and "t" tests.

Results

A number of factors have been analyzed (Table I) to establish that the treated and untreated groups were comparable. These factors include age, weight, history of hypertension, history of valvular heart disease, history of cerebrovascular accidents, history of diabetes, history of claudication, family history of coronary disease, cerebrovascular disease or claudication, previous myocardial infarction, collapse at onset of illness, cardiomegaly, acute pulmonary edema, clinical shock (systolic blood pressure below 80 mm. Hg and cold clammy skin or oliguria), physical signs of congestive heart failure, the use of digitalis, quinidine and Pronestyl during the hospitalization and the occurrence of ventricular premature contractions. Ventricular premature contractions greater than 1 per 10 (Table I) indicate that at some time during hospitalization the patient was shown to have more than one ventricular premature contraction per 10 beats. There was no significant difference between the treated and the untreated group in the frequency of any of the above mentioned factors. However, there was a statistically significantly higher incidence of a history of congestive heart failure prior to hospitalization and of the duration of this congestive heart failure in the untreated group (40 per cent) than in the treated group (18 per cent). This would be expected to influence the results in the direction of a higher mortality in the untreated group.[7]

Of the total 147 patients, 27 died, an over-all mortality rate of 18 per cent. This mortality rate, somewhat lower than other reported values,[11] was probably due to the fact that (1) the patients frequently were seen initially by a referring physician with delay before admission and (2) they were included in the study only if they survived until arrival on the cardiovascular ward. The mortality rates in the three groups were: 21 per cent in those receiving no anticoagulants, 17 per cent in those adequately coagulated, and 13 per cent in those designated as inadequately treated. The differences in the mortality rates in the three groups are not significant (.70 > p > .50). Nine of the total of 27 deaths occurred in the first 48 hours after admission of the patient for acute myocardial infarction, and 8 of these deaths occurred in the untreated group. It has frequently been stated that antithromboembolic therapy should not be expected to alter the incidence of early deaths (first 24 to 48 hours).[2,3,4] Data are often presented separately for patients surviving beyond the first 2 days. In this study, when the deaths which occurred in the first 48 hours are omitted (Table III), the mortality rate is considerably lowered in the untreated patients. Thus, if one considers only those patients surviving the first 48 hours of hospitalization, the mortality rate is 11 per cent in the untreated group and 14 per cent in the treated group. These differences are again not statistically significant.

As shown in Tables II and IV, the lowest mortality rate occurred in the inadequately treated group. Comparison of the factors

Table II. Influence of anticoagulant therapy on mortality

	No anti-coagulation	Total anticoagulation	Adequate anticoagulation	Inadequate anticoagulation
Number of patients	70	77	46	31
Number of deaths	15	12	8	4
Per cent mortality	21	16	17	13

Table III Mortality rates in the first 48 hours after hospitalization for acute myocardial infarction

	No anticoagulation	Total anticoagulation
Number of deaths	8	1
Per cent mortality	11	1

which might affect mortality (Table I) showed a lower incidence of congestive heart failure previous myocardial infarctions, acute pulmonary edema and cardiomegaly and a lower mean age in this group At the same time, the highest percentage of shock collapse past history of diabetes mellitus, cerebrovascular accidents, and arteriosclerosis obliterans occurred in this group. These differences however are not statistically significant

Table IV Influence of various grades of anticoagulant therapy on mortality after the first 48 hours

	No anticoagulation	Total anticoagulation	Adequate anticoagulation	Inadequate anticoagulation
Number of patients	62	76	46	30
Number of deaths	7	11	8	3
Per cent mortality	11	14	17	10

Table V Influence of various degrees of anticoagulation on mortality thromboembolism and hemorrhage in the good risk patients

	No anticoagulation	Total anticoagulation	Adequate anticoagulation	Inadequate anticoagulation
Number of patients	21	31	18	13
Number of deaths	0	0	0	0
Per cent mortality	0	0	0	0
Per cent of thromboemboli	0	0	0	0
Number of patients with hemorrhages	0	1	1	0
Per cent with hemorrhages	0	3	6	0

Table VI Influence of various degrees of anticoagulation on mortality thromboembolism and hemorrhage in the bad risk patients

	No anticoagulation	Total anticoagulation	Adequate anticoagulation	Inadequate anticoagulation
Number of patients	49	46	28	18
Number of deaths	15	12	8	4
Per cent mortality	31	26	29	22
Number of patients with thromboemboli	2	1	0	1
Per cent of thromboemboli	4	2	0	6
Number of patients with hemorrhages	6	12	6	6
Percent of hemorrhages	12	26	21	33

A simple explanation for the lower mortality in this group is not apparent. It is possible that the attending physicians noted that the patients were doing well and were not so forceful in the application of anticoagulant therapy.

The patients in this study were also analyzed according to Russek's criteria as to "good risk" and "bad risk."[9] The results are given in Tables V and VI. Fifty-two patients met the "good risk" criteria (35 per cent of the group) and 95 patients were in the "bad-risk" category (65 per cent). No patients in the "good risk" group died. However, in the "bad risk" group there was no significant difference in the mortality between the treated and untreated patients.

Tables V, VI, and VII note the thromboembolic and hemorrhagic complications detected during the course of acute myocardial infarction in these patients. Of the 19 patients with hemorrhagic manifestations, 18 were in the "bad risk" group. Hemorrhagic complications were twice as common in the treated as in the untreated patients, but the difference is again not statistically significant. The infrequency of hemorrhagic complications in the "good risk" patients might suggest that these patients can be treated with anticoagulants with little risk. On the other hand the absence of thromboembolic complications and of mortality would tend to substantiate the opinion of Russek and his colleagues that such therapy is not warranted in "good risk" patients.[9,10]

Table VIII lists the sites and frequency of hemorrhages in the three groups. Only one instance of hemorrhage resulted in death, and this was in a patient in the untreated group who died as a result of rupture of the myocardium with hemorrhage into the pericardium.

There were only three clinically detected thromboembolic episodes (Table VI). One patient in the inadequately treated group developed signs of embolism to the lungs, spleen, and mesentery, but after 5 weeks of hospitalization he was discharged with no apparent sequelae. In the untreated group, one patient with a pulmonary embolus survived without consequences, and one with a cerebral embolus did not survive. Although this death was ascribed to pneumonia, the cerebral infarction was a major factor in it.

Discussion

This study does not suggest that anticoagulants are of value in lowering the mortality rate in acute myocardial infarc-

Table VII. *Influence of various degrees of anticoagulation on hemorrhage*

	No anticoagulation	*Total anticoagulation*	*Adequate anticoagulation*	*Inadequate anticoagulation*
Number of patients	70	77	46	31
Number of hemorrhages	6	13	7	6
Per cent of hemorrhages	9	17	15	19

Table VIII. *Location and number of hemorrhages in each group of "bad risk" patients*

Location of hemorrhage	*No anticoagulation*	*Adequate anticoagulation*	*Inadequate anticoagulation*
Urine	3	3	0
Lung	1	1	1
Gastrointestinal	0	1	3
Pericardium	2	1	1
Gingiva	0	0	1

tion In a larger study Hilden and associates[3] reported on their 4-year program involving 800 patients with acute myocardial infarction 371 of these were treated with anticoagulants and 429 were not. The total mortality in the anticoagulated patients was 22 0 per cent, and that in the *nonanticoagulated patients* was 25 4 per cent, a difference which was not statistically significant

In a subsequent review Iversen and Hilden[12] reviewed 25 previous studies of the influence of anticoagulation on the course of acute myocardial infarction They found 15 of these studies to be unacceptable because of the lack of comparability between the treated and untreated patients, whereas 10 studies in addition to their own were found to be acceptable on this basis of comparability but 4 of these were criticized on other bases. They were particularly critical of the largest reported study that of Wright, Marple and Beck,[1] especially with regard to the unequal size of the treated and control groups and to the basis for assignment of patients to control or treatment groups. Furthermore they pointed out that if one considered only ward service patients in Wright s study the difference in mortality was only 4 8 per cent whereas in the total series the difference in mortality was 7 4 per cent. Moreover if those hospitals in Wright s study which had only ward service patients were considered there was no difference at all in the mortality rate between the treated and untreated group Iversen and Hilden implied therefore that bias in the selection of patients on the private services might have accounted for some of the differences in mortality between anticoagulated and control groups

The study herein reported would appear to avoid the major criticisms of Iversen and Hilden.[12] As indicated in Table I the groups were comparable, with the exception of the increased incidence of previous congestive heart failure in the untreated patients. The groups were treated during the same period of time, and care was offered in the same ward by the same group of physicians. There were no irregularities in regard to admission of patients to the improper group

Russek and Zohman[9] believe that the use of anticoagulants should be limited to selected cases the bad risk patients, who are those with (1) previous myocardial infarction (2) intractable pain (3) extreme degree or persistence of shock (4) significant enlargement of the heart, (5) gallop rhythm (6) congestive heart failure, (7) auricular fibrillation or flutter ventricular tachycardia or intraventricular block (8) diabetic acidosis, or other states predisposing to thrombosis. Division of the patients in our study did indeed indicate low mortality in the good risk patients, since there were no deaths in this group. On the other hand anticoagulant therapy (Table VI) did not influence the mortality in the bad risk group. From this study then it would appear that the division of patients into good risk and bad risk cases would serve only as an aid in prognosis, but that neither group would benefit from the routine administration of anticoagulants.

If it is accepted as suggested by Seaman[14] that prophylactic anticoagulant therapy is valuable in preventing venous thrombi and emboli but not arterial thrombotic disease then mortality could be significantly affected only if such venous thromboembolism were a significant factor in the mortality of patients with acute myocardial infarction Thromboembolism was detected so infrequently in the patients of this study that therapy altering the incidence of thromboembolism could not be expected to alter over-all mortality Autopsies were performed on 12 of the 27 patients who died In all of these, the clinical impression of the absence of thromboembolism was confirmed (and the presence of myocardial infarction was also confirmed) The infrequency of thromboembolism in the patients of this study particularly as contrasted with the findings in earlier reports,[1] is believed to be related to the avoidance of excessive sedation the early bed-and-chair state of activity the encouragement of leg motion and the allowance of ambulation at 3 weeks. If anticoagulant therapy is indeed of value in preventing venous thrombosis and pulmonary embolism it should be used in patients with acute myocardial infarction only on the basis of the same indications

for which it would be employed in any patient subjected to a prolonged period of inactivity. The infrequency with which anticoagulant therapy is used in patients subjected to prolonged rest for conditions other than acute myocardial infarction would suggest that it is rarely indicated in any patients as a prophylactic measure.

This study suggests that factors other than those affected by anticoagulants must influence the prognosis in the first weeks of acute myocardial infarction. The use of anticoagulants as a routine measure in these circumstances is not supported.

Summary

1. The effect of anticoagulation therapy on mortality and morbidity in 147 consecutive male patients with acute myocardial infarction was evaluated.

2. The patients were divided into three groups: those adequately anticoagulated, those inadequately anticoagulated, and those not anticoagulated. The patients were randomly assigned and the groups were shown to be comparable, except for an increased incidence of a history of previous heart failure in the untreated group.

3. There was no significant reduction in mortality in the anticoagulated groups when compared to the control group.

4. The incidence of thromboemboli was too low to be of significance in assessing the effects of anticoagulants as antithrombotic agents.

5. We conclude from this study that routine anticoagulation therapy is not indicated in acute myocardial infarction and that factors other than those affected by anticoagulants determine the prognosis in this disease.

We wish to express our appreciation for the assistance rendered by the resident physicians assigned to the Cardiovascular Ward and by the personnel of the automatic Data Processing Section of the Veterans Administration Hospital, Richmond, Va.

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tion. In a larger study, Hilden and associates[8] reported on their 4-year program involving 800 patients with acute myocardial infarction: 371 of these were treated with anticoagulants and 429 were not. The total mortality in the anticoagulated patients was 22.0 per cent, and that in the nonanticoagulated patients was 25.4 per cent, a difference which was not statistically significant.

In a subsequent review, Iversen and Hilden[12] reviewed 25 previous studies of the influence of anticoagulation on the course of acute myocardial infarction. They found 15 of these studies to be unacceptable because of the lack of comparability between the treated and untreated patients, whereas 10 studies in addition to their own were found to be acceptable on this basis of comparability, but 4 of these were criticized on other bases. They were particularly critical of the largest reported study, that of Wright, Marple and Beck,[1] especially with regard to the unequal size of the treated and control groups and to the basis for assignment of patients to control or treatment groups. Furthermore, they pointed out that if one considered only ward-service patients in Wright's study, the difference in mortality was only 4.8 per cent, whereas in the total series the difference in mortality was 7.4 per cent. Moreover, if those hospitals in Wright's study which had only ward-service patients were considered, there was no difference at all in the mortality rate between the treated and untreated group. Iversen and Hilden implied, therefore, that bias in the selection of patients on the private services might have accounted for some of the differences in mortality between anticoagulated and control groups.

The study herein reported would appear to avoid the major criticisms of Iversen and Hilden.[12] As indicated in Table I, the groups were comparable, with the exception of the increased incidence of previous congestive heart failure in the untreated patients. The groups were treated during the same period of time, and care was offered in the same ward by the same group of physicians. There were no irregularities in regard to admission of patients to the improper group.

Russek and Zohman[9] believe that the use of anticoagulants should be limited to selected cases, the "bad risk" patients, who are those with: (1) previous myocardial infarction, (2) intractable pain, (3) extreme degree or persistence of shock, (4) significant enlargement of the heart, (5) gallop rhythm, (6) congestive heart failure, (7) auricular fibrillation or flutter, ventricular tachycardia, or intraventricular block, (8) diabetic acidosis or other states predisposing to thrombosis. Division of the patients in our study did indeed indicate low mortality in the "good risk" patients, since there were no deaths in this group. On the other hand, anticoagulant therapy (Table VI) did not influence the mortality in the "bad-risk" group. From this study, then, it would appear that the division of patients into good-risk and bad-risk cases would serve only as an aid in prognosis, but that neither group would benefit from the routine administration of anticoagulants.

If it is accepted, as suggested by Seaman,[13] that prophylactic anticoagulant therapy is valuable in preventing venous thrombi and emboli, but not arterial thrombotic disease, then mortality could be significantly affected only if such venous thromboembolism were a significant factor in the mortality of patients with acute myocardial infarction. Thromboembolism was detected so infrequently in the patients of this study that therapy altering the incidence of thromboembolism could not be expected to alter over-all mortality. Autopsies were performed on 12 of the 27 patients who died. In all of these, the clinical impression of the absence of thromboembolism was confirmed (and the presence of myocardial infarction was also confirmed). The infrequency of thromboembolism in the patients of this study, particularly as contrasted with the findings in earlier reports,[1] is believed to be related to the avoidance of excessive sedation, the early bed-and-chair state of activity, the encouragement of leg motion, and the allowance of ambulation at 3 weeks. If anticoagulant therapy is indeed of value in preventing venous thrombosis and pulmonary embolism, it should be used in patients with acute myocardial infarction only on the basis of the same indications

responses to various drugs of rats with genetic hypertension have been compared with the responses of rats with experimental renal hypertension of the Goldblatt type.

Methods

Preliminary treatment and selection of animals Renal hypertension was induced in male albino Wistar rats from the Otago stock colony weighing approximately 250 grams by applying a silver clip (0 0095 inch in diameter) to the left renal artery [9] The right kidney remained intact. Ten to 20 weeks later the animals were used for experiments. Systolic blood pressures were measured by a modification of the tail-cuff method of Gallagher and Grimwood [10] and expressed as the mean of three readings made at 2-day intervals. An equal number of rats from the same colony used as a control group underwent a dummy operation in which the renal artery was exposed but not clipped

Chronic renal hypertensive rats (CR rats) and dummy-operated control rats (DC rats) matched for weight and age were paired for use in the first series of experiments. Results obtained from 3 of the approximately 200 rats used were discarded because of imperfections in technique.

Rats with inherited hypertension (B rats) were matched for weight, age and blood pressure with CR rats. When controls were used for this group they were weight matched rats not operated upon from the Otago stock colony

Experimental procedure Cannulation of a femoral vein and of the trachea of the pairs of rats was performed under ether anesthesia chloralose (50 mg per kilogram) was then given intravenously to maintain anesthesia. After 20 minutes, when hemostasis had occurred, a femoral artery was cannulated and heparin (1 000 units) was given as an anticoagulant. Direct mean blood pressures were measured from the cannulated femoral artery using a small-volume mercury manometer and kymographic recording

Drugs were injected into the cannulated femoral vein in 0 1 ml of normal saline and washed in with an equal volume of saline. Pressor drugs were administered at 10-minute intervals, and the means of at least two responses to angiotensin and norepinephrine were used. A single dose only of vasopressin was given always as the last injection because of the slow recovery from the pressor effect and the possible occurrence of tachyphylaxis. In the experiments in which hexamethonium was given a single injection of norepinephrine was made as soon as the maximum fall in blood pressure had been clearly established in each rat of a pair

The drugs used were norepinephrine bitartrate (Levophed Winthrop) 0.35 μg of base per kilogram vasopressin (Pitressin, Parke Davis) 0 133 units per kilogram synthetic angiotensin val[5]-amide (Ciba 19990*) 0 167 μg per kilogram, and hexamethonium bromide, 17 mg per kilogram

Results

Effect of pressor agents on the blood pressure of rats with chronic renal hypertension and of dummy-operated controls Synthetic angiotensin was administered to 59 CR rats and 58 DC rats (Fig 1) vasopressin to 47 CR rats and 46 DC rats (Fig 2) and norepinephrine to 66 pairs of CR and DC rats (Fig 3) The rise in blood pressure was plotted against the blood pressure immediately before the injection of each drug When angiotensin or vasopressin was used, higher initial blood pressures were associated with smaller pressor responses. The correlation between pressor response and initial blood pressure for each of these drugs was significant for both renal hypertensive rats ($p < 0\ 001$) and for controls ($p < 0\ 01$)

The regression lines for angiotensin and vasopressin of the CR rats lie above those for the controls but the difference in reactivity over any range of blood pressures reached significant levels only for vasopressin. By comparison of the error functions of the two regression lines it was found that, for initial pressures of less than 155 mm. Hg the responses of CR rats to vasopressin were significantly greater than the responses of DC rats ($p < 0\ 02$)

The responses to norepinephrine exhibit an interesting difference from the responses to angiotensin and vasopressin In CR rats with pressures up to 170 mm Hg (the upper level for genetic hypertensive rats) and in DC rats the pressor responses to the neurotransmitter norepinephrine, were not influenced significantly by the

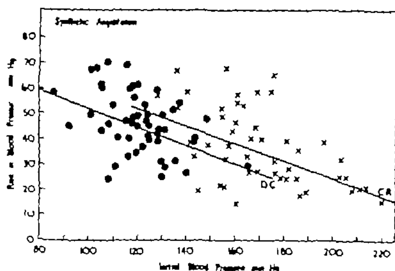


Fig 1 Relationship between initial blood pressure and rise in blood pressure with injected synthetic angiotensin for CR rats (*crosses*) and DC rats (*solid dots*). The regression lines for CR rats ($r = -0.501$ $p<0.001$) and DC rats ($r = -0.394$ $p<0.01$) are both significant.

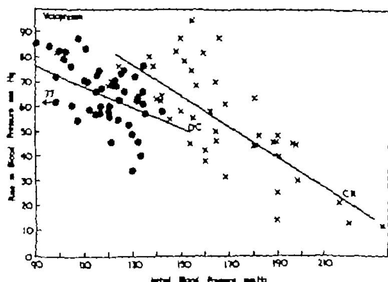


Fig 2 Relationship between initial blood pressure and rise in blood pressure with injected vasopressin for CR rats and DC rats. Symbols as in Fig 1 The regression lines for CR rats ($r = -0.789$ $p<0.001$) and DC rats ($r = -0.459$ $p<0.01$) are both significant.

level of the initial pressure (Fig 3) When however the initial blood pressure of CR rats exceeded 170 mm Hg there was a decrease in the pressor response to norepinephrine as initial pressures rose to still higher levels Furthermore, when the mean pressor response to norepinephrine (35 6 mm.Hg) of the 31 CR rats with blood pressures less than 170 mm Hg (mean blood pressure 151 8 mm.Hg) was compared with the mean response of the 66 DC rats (36 1 mm Hg) the values did not differ significantly ($p > 0.8$) If CR rats with initial pressures higher than 170 mm.Hg are included the mean pressor response of the 66 CR rats was 30 4 mm Hg with a mean initial pressure for the group of 176 6 mm Hg and the corresponding value for the DC rats was 36 1 mm.Hg with an initial blood pressure of 120 4

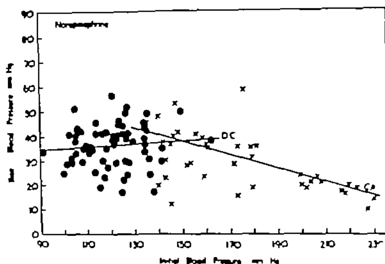


Fig 3 Relationship between initial blood pressure and rise in blood pressure with injected norepinephrine for CR rats and DC rats. Symbols as in Fig 1 The regression line for CR rats is significant ($r = -0.569$ $p<0.001$) but is not significant for DC rats ($r = 0.083$ $p>0.6$). When only the 31 CR rats with initial blood pressures less than 170 mm. Hg are considered, the correlation coefficient is not significant ($r = 0.130$ $p>0.3$)

mm.Hg this difference between the pressor responses to norepinephrine is significant ($p < 0.01$)

Effect of hexamethonium on the blood pressure and on the response to norepinephrine of chronic renal hypertensive rats and of controls Immediately before the administration of hexamethonium bromide the mean blood pressure of 30 renal hypertensive rats was 181 0 mm. Hg and that of 29 control rats was 117 1 mm.Hg after hexamethonium the corresponding blood pressures were 88.2 and 69.8 mm. Hg respectively This latter difference in the average levels of the blood pressure after a large dose of hexamethonium the hexamethonium floor is significant ($p < 0.001$) Higher initial pressures were associated with larger falls in blood pressure, the correlation between fall in blood pressure and blood pressure being significant for both CR rats ($p<0.001$) and for DC rats ($p<0.02$)

Hexamethonium changed the relation ship between the pressor responses to norepinephrine of CR and DC rats Thus, after hexamethonium, the pressor response of 28 CR rats was 72 4 mm Hg and that of 27 DC rats was 61 9 mm.Hg The pressor responses after hexamethonium were now significantly greater in CR than in DC rats ($p<0.001$)

Comparison of the effects of pressor agents and hexamethonium in rats with spontaneous inherited hypertension and those with chronic renal hypertension

A. PRESSOR DRUGS The results of administering norepinephrine angiotensin, and vasopressin to pairs of rats with inherited hypertension matched for weight, age, and blood pressure with rats with renal hypertension are set out in Table I Only with vasopressin is the response of CR rats significantly greater than the response of B rats.

B EFFECT OF HEXAMETHONIUM ON THE BLOOD PRESSURES OF RATS WITH INHERITED HYPERTENSION THOSE WITH CHRONIC RENAL HYPERTENSION AND CONTROLS Hexamethonium bromide (17 mg per kilogram) was given to 25 pairs of rats with inherited hypertension (mean blood pressure of 151 8 mm.Hg) and with experimental renal hypertension (mean blood pressure of 156 8 mm Hg) and also to 26 control rats not operated upon (mean blood pressure of 122.0 mm Hg) The means of the floor blood pressures after hexamethonium bromide were 78.0 87 4 and 67.5 mm Hg respectively The blood pressure after hexamethonium of both B and CR rats was significantly higher than that of the control rats ($p<0.02$) also, the mean floor blood pressure of the CR rats was

Table I. Comparison of pressor responses in rats with inherited hypertension and those with renal hypertension matched for weight, age, and blood pressure

Drug	Blood pressure (mm. Hg)		Response (mm. Hg)		Significance of difference between responses
	B	CR	B	CR	
Norepinephrine (10)*	149.5	153.8	40.8	39.7	$p > 0.8$
Angiotensin (11)*	151.8	152.4	34.7	37.4	$p > 0.6$
Vasopressin (25)	149.5	154.0	50.1	65.1	$p < 0.001$

*Number of pairs of rats.

Table II. Effect of hexamethonium on the blood pressure of rats with inherited hypertension, those with renal hypertension, and controls

	Blood pressure before hexamethonium (mm. Hg)	Hexamethonium floor pressure (mm. Hg)	Significance of difference	Neurogenically maintained part of the blood pressure* (mm. Hg)
Renal hypertensive (15)†	158.5	91.8		66.7
			$p < 0.05$	
Genetic hypertensive (15)	156.5	80.1		76.4
			$p < 0.02$	
Control normotensive (26)	122.0	67.5		54.5

	Blood pressure increase above control level (mm. Hg)	Not neurogenically maintained part of blood pressure increase (mm. Hg)	Neurogenically maintained part of blood pressure increase (mm. Hg)
Renal hypertensive (15)	36.5	24.3	12.2
Genetic hypertensive (15)	34.5	12.6	21.9
Significance of difference	$p > 0.5$	$p < 0.05$	$p < 0.05$

*That part of the blood pressure which is removed by blockade of the sympathetic nerves.
†Number of rats.

significantly higher than that of the B rats ($p < 0.05$).

Since the latter result could have been due to the slightly higher initial blood pressure of the renal hypertensive rats, a separate analysis was made of the response to hexamethonium in the 15 pairs of rats whose initial blood pressures matched most closely, i.e., within 5 mm. Hg. An important difference remained between the responses of genetic and of renal hypertensive rats to hexamethonium which is summarized in Table II.

In the genetic hypertensive rats the major part of the increase in blood pressure is removed by hexamethonium, whereas this is not true for the rats with chronic renal hypertension. This difference is significant.

After hexamethonium the pressor responses to norepinephrine of the same 10 pairs of B and CR rats whose responses before ganglion blockade are shown in Table I still did not differ significantly.

Discussion

The primary aim of this paper was to compare cardiovascular reactivity in rats with spontaneous inherited hypertension (B rats) and those with renal hypertension (CR rats). It has already been shown that the responses of B rats to a

number of drugs are dependent on the blood pressure at the time the drugs are administered[7] and it has now been demonstrated that the responses of CR rats are similarly dependent on the blood pressure. The most valid comparison of responses, therefore, to substances affecting blood pressure is that made when the blood pressures of the animals before the administration are similar. But when comparisons are made between hypertensive and normotensive animals, the blood pressures are of necessity dissimilar. The interpretation of results, however, may be aided by regression analysis, although it is rarely possible to show that the data truly fit a linear regression or that extrapolation beyond the measured values is valid. Other workers also have found that cardiovascular responses depend on the blood pressure[11,12] and that a high initial level of blood pressure, as such, tends to decrease the responses to pressor reflexes.[13]

When whole-animal blood pressure responses to vasoactive agents are being studied, it is not easy to distinguish the changes in blood pressure secondary to alterations in cardiac performance from those caused by a more direct action on the peripheral vascular bed.[14] Nevertheless, change in arterial pressure under standard conditions remains a convenient parameter to measure[5,15] and when interpreted with due care yields useful information.

In experimental hypertension an increased responsiveness of the cardiovascular system as a whole or of discrete portions of it has been demonstrated by various workers.[16] Enhanced pressor reactivity in experimental hypertension has been found both before[7,18] and after ganglion blockade.[19]

Whether the increased cardiovascular reactivity of B rats and CR rats to vasopressin and to norepinephrine after ganglion blockade is due to greater intrinsic sensitivity of the vascular smooth muscle in hypertension,[21] hypertrophy[22,23] or engorgement of the vessel walls,[7] or to other factors involving the heart or central nervous system cannot be decided by the present experiments. Although there may be some structural change such as hypertrophy of smooth muscle, there is no evidence of any increased peripheral resistance in the denervated hind limbs of CR or B rats[24] which would be expected if the enhanced peripheral resistance in hypertension were due to structural changes in the vessel walls limiting the amount of vasodilation which could occur.[24,25]

Enhanced cardiovascular reactivity is not necessarily dependent on hypertension and exists, for instance, in the prehypertensive phase of renal hypertension.[26-31] In coarctation of the aorta, the perfused hindquarters of rats had an enhanced reactivity to norepinephrine although the blood pressure below the constriction had remained normal.[32] Rats with a genetic predisposition to develop hypertension in response to the administration of salt or to renal artery constriction exhibit also a cardiovascular hyperreactivity to norepinephrine and angiotensin.[33]

Nevertheless, the results presented in this paper show that, in rats, at least two hypertensive states, genetic hypertension and chronic renal hypertension, and the degree of hypertension can modify cardiovascular reactivity.

As yet few genetic hypertensive rats have blood pressures higher than 170 mm Hg and consequently it is only below this level that the response of B and CR rats can be compared directly. The magnitude of the responses to angiotensin and vasopressin is strongly dependent on the blood pressure, but up to 170 mm Hg the responses to norepinephrine are independent of the level of the blood pressure. Above this level the responses of CR rats to norepinephrine diminish with further increases in the level of the blood pressure. The responses to angiotensin and to norepinephrine of rats with genetic hypertension and with renal hypertension matched closely for blood pressure do not differ significantly. Furthermore, the responses to norepinephrine of B rats[7] and of CR rats are no greater than the responses of controls, and this cannot be attributed to a difference in the levels of blood pressure.

Both B and CR rats exhibit an enhanced reactivity above the normal to vasopressin which is more marked in renal hypertension than in genetic hypertension. An increased responsiveness to vasopressin has been found previously in experimental renal

hypertension[illegible] and in adrenal regeneration hypertension.[31]

Laverty and Smirk[illegible] and Phelan and associates[7] had earlier found that chronic renal hypertensive rats had a higher blood pressure after ganglion blockade than did rats with inherited hypertension but in neither case did the blood pressure of the B rats differ from that of controls after the administration of hexamethonium. Since these experiments, the mean blood pressure of the genetic hypertensive colony has been raised and a *non neurogenically maintained* component of the blood pressure has appeared. The present series of experiments *confirms the earlier findings that the neurogenically* maintained fraction of the blood pressure namely, that part of the blood pressure elevation which is removed by blockade of the nervous system,[illegible] is largely responsible for the raising of the blood pressure to hypertensive levels in B rats and also, is important in CR rats.

It seems to be possible that as the blood pressures in the genetic colony reach higher levels inherited spontaneous and renal hypertension will show closer relationships, but initially the nervous system plays a more important part in the pathogenesis of the former than of the latter.

Summary

The cardiovascular responses to pressor *drugs and ganglion blockade were examined* in rats with spontaneous inherited hypertension and rats with renal hypertension. Similarities and differences in the reactions *of the two types of rats were observed. The* differences, with other evidence, indicate that the pathogenesis of spontaneous in*herited hypertension differs from that of* chronic renal hypertension.

The blood pressure immediately prior to injection affected the magnitude of the response to vasopressin and angiotensin of rats with inherited hypertension, rats with chronic renal hypertension, and controls at all levels of the blood pressure. Within any one of these groups, higher blood pressures were associated with smaller pressor responses. Therefore the importance of making allowance for differing levels of blood pressure when one is comparing cardiovascular reactivity is stressed.

The responses to vasopressin of rats with inherited hypertension were significantly less than those of renal hypertensive rats with closely comparable blood pressures. The responses of renal hypertensive rats were significantly greater than those of controls.

The pressor responses to angiotensin of rats with inherited hypertension, of those with renal hypertension, and of controls did not differ significantly.

When the initial blood pressures were *less than 170 mm. Hg (the upper level of* blood pressures commonly encountered in rats with inherited hypertension) the *responses to norepinephrine of rats with* inherited hypertension, of those with renal hypertension, and of controls showed no correlation with the blood *pressure* and did not differ significantly. In renal hypertensive rats with blood pressures greater than 170 mm. Hg the pressor responses to norepinephrine decreased with increasing blood pressure.

After ganglion blockade with hexamethonium the blood pressure fell to a significantly lower level in rats with inherited hypertension than in rats with renal hypertension, and in both cases the blood pressure after hexamethonium was higher than that of control rats. The extent of the fall was dependent on the initial level of the blood pressure.

The neurogenically maintained component of the blood pressure which was removed by ganglion blockade was mainly responsible for the elevation of the blood *pressure to hypertensive levels in rats with* inherited hypertension. At closely similar levels of the blood pressure the neurogenically maintained fraction of the blood pressure accounted for approximately 60 per cent of the elevation of the blood pressure above control levels in rats with inherited hypertension, and for only 30 per cent of the excess in renal hypertensive rats.

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The vascular supply of the left ventricular wall

Anatomic observations, plus a hypothesis regarding acute events in coronary artery disease

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The concept that the clinical syndrome of coronary artery disease is accompanied by a well-defined anatomic explanation is widely taught and widely accepted. A closer look reveals many puzzling discrepancies. Among these are the following:

1. Lack of quantitative relationship between the anatomic lesion and the clinical symptoms of coronary disease.[1] Some patients suffer major myocardial necrosis and death with minor occlusive disease of the coronary vessels, whereas others have multiple and severe anatomic occlusions with no clinical symptoms.

2. Lack of a temporal relationship between coronary occlusive disease and acute clinical events.[1,2] Many patients with acute infarction are found to have large vessel occlusions of considerable age with no fresh lesion to account for the acute event.

3. Day-to-day variability in severity of clinical symptoms. Most patients with angina experience "good" and "bad" days. A given physical task performed with ease on a "good" day will result in severe pain on a "bad" day.

4. The frequent lamellar distribution of myocardial infarcts within the ventricular wall.[3] Whereas many infarcts involve an entire thickness of ventricular wall, many others distribute themselves in a layer surrounded by apparently viable muscle and with *no apparent correlation* with the known distribution of coronary vessels.

These puzzling facts seem to point to unknown dynamic factors, in addition to anatomic disease of the coronary vessels, as a cause of the acute clinical events in this disease.

Over the past 2 years we have studied the coronary arteries by means of post-mortem angiograms and detailed gross

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and histologic examination in a group of 120 hearts obtained at autopsy. In the last 58 of these hearts detailed studies of the vessels of the left ventricular free wall have been carried out. These have revealed features of the arterial supply to the left ventricular wall which suggest a possible means of dynamic control of coronary arterial blood flow by myocardial contraction itself and provide a possible explanation for the discrepancies noted above. This new hypothesis assigns a "permissive" role to the major anatomic lesions of the coronary arteries. When such lesions are present, the control of flow through small myocardial vessels becomes of critical importance to the total integrity of myocardial blood supply, determining the occurrence of acute clinical events and the distribution of myocardial ischemic damage within the ventricular wall.

Methods

The selection of case material for this study was largely a random process although certain cases were chosen because of the known presence of heart disease, plus the interest of the patient's physician or the prosector in the detailed observations which characterized the study. This accounts for a high percentage of cases of heart disease. Most patients were adults, although some children were included. The ages ranged from 2 months to 80 years. Clinical diagnosis are noted in Table I.

At autopsy, the heart was removed and cannulae were tied into the right and left coronary arteries at their origin. The coronary bed was flushed with saline for 10 minutes, after which the coronary arteries were filled with a barium-gelatin mass similar to that described by Schlesinger but using a barium sulfate of smaller particle size (Micropaque*). The injection was carried out at room temperature for a period of 20 minutes at a pressure of 100 millimeters of mercury. The injection mass did not pass through the capillary bed and never emerged from the venous channels. The heart was cooled to hasten solidification of the injection mass, and stereoscopic anteroposterior and lateral radiographic exposures were made at a 40-inch tube-film distance. These radiographs served as a guide for a detailed dissection of the large coronary vessels which was carried out after 24 hours of fixation in 10 per cent formalin. The myocardium was also carefully observed and all lesions were recorded.

Several regions of myocardium received special attention, in that they were removed and studied in more detail both radiographically and microscopically. One such region was the upper interventricular septal area containing the A-V node and large conduction pathways. The other was the left ventricular wall and papillary muscles. Longitudinal sections of the left ventricular wall from valve ring to apex, were obtained usually from both the area of the anterolateral papillary muscle and the posteromedial papillary muscle. These measured from 1 to 2 cm. in thickness. Stereoscopic radiographic exposures of each such area removed were made using a beryllium window industrial x-ray unit and technique similar to that described by Hale and Reed. Exposures were usually made at a 12-inch tube-film distance with the specimen directly on the film packet. Exposures were made for 2 minutes at 6 milliamperes and 20 to 25 kilovolts using Eastman type M film. More recently an underwater technique, as described by Fulton,[8] has also been used. After the radiographic exposures, the specimen was then submitted for microscopic sectioning or stored for future reference. The radiographs constitute the material from which these observations are derived. Vessel size was determined by direct measurement of size in 4X enlargements of these radiographs.

Table I *Clinical diagnosis in 58 cases*

No heart disease	21
Coronary artery disease	20
Hypertensive cardiovascular disease	6
Hypertensive cardiovascular disease plus coronary artery disease	4
Congenital heart disease	3
Rheumatic heart disease	2
Myocarditis	2

*Damancy and Company Ltd., obtained through Picker X-Ray Corp.

Results

The large epicardial coronary vessels leave the A V ring and course in a base-to-apex direction over the epicardial surface of the heart These large epicardial vessels divide on the surface and after reaching a size of 1 to 3 mm they begin to send deep tributaries at right angles into the myocardium (See Figs 1 3) These tributaries are 400 to 1 500 microns in diameter and they in turn, quickly subdivide The subdivisions are of two general classes The vessels of one class (Class A) quickly branch into a very fine network which distributes itself in the outer three fourths to four fifths of the myocardium The vessels of the other class (Class B) are less numerous, branch infrequently and reach the inner layers of the myocardium with at most no reduction in size. Indeed many such vessels are seen to enlarge as they approach the endocardium (Fig 3) At or near the subendocardium these vessels subdivide forming large looping arcades which can be seen in stereoscopic views to anastomose freely in the subendocardial layers. These anastomosing arcades form a large subendocardial plexus of vessels which is fed at multiple points by Class B vessels derived from many epicardial vessels

The Class B vessels and the subendocardial plexus range in size from 50 to 500 microns, with occasional arcades in the plexus reaching 1 000 microns in size. The subendocardial plexus was seen in 56 of the 58 hearts examined The exception was that from a 54-year-old man with a



Fig. 1 Radiograph of left ventricular free wall from a 52-year-old man who died of acute arsenic intoxication There was no coronary occlusive disease and no valvular or myocardial abnormality The epicardial surface is to the right. The tip of a papillary muscle can be seen at the lower margin on the left. The Class A vessels are seen as fine, delicately branching vessels, which are distributed in the outer three fourths of the wall. The Class B vessels are large, and form large arcades just beneath the endocardial surface. (Enlarged ×3)

20-year history of hypertension who died of renal failure. He had cardiomegaly (heart weight of 550 grams) with marked concentric hypertrophy but there were no coronary occlusive lesions. In spite of excellent filling of the large epicardial vessels, there was poor filling of myocardial vessels of both Class A and Class B types. The Class B vessels were of small diameter and did not fill beyond the junction of the middle and inner thirds of the myocardium

In children and young adults the subendocardial plexus tends to be formed of delicate vessels of small diameter but there are striking exceptions as seen in Fig 2. The vessels forming the subendocardial plexus are often exceptionally large in hearts with occlusive disease of the coronary arteries.

In addition, coronary artery disease produces various alterations in the basic arrangement described above. In zones of fibrosis (see Figs 4 and 5) there is a dense "feltwork" of very fine vascular channels. This interrupts the regular arrangement of Class A vessels which are normally aligned perpendicular to the epicardial surface. In many such cases the subendocardial plexus and Class B vessels appear to be unaffected In regions of heavy scar formation the vessels are occasionally seen to be completely obliterated



Fig. 2 Radiograph of left ventricular free wall from a 17-year-old boy who died of renal failure as a complication of paroxysmal nocturnal hemoglobinuria. The epicardial surface is to the right. Note the large size of the Class B vessels and the subendocardial plexus, some of which measured 500 microns in diameter There were a few small focal fibrotic lesions in the myocardium, but the coronary vessels were normal. (Enlarged ×3)

in an entire portion of myocardium In such cases the process involves both Class A and Class B vessels in a laminar region and there are no direct epicardial to-endocardial connections through the area (see Figs. 6 and 7) Instead the vessels assume a longitudinal arrangement parallel with the epicardial and endocardial surfaces. The surviving zones of muscle in the subendocardial region receive their vascular supply through enlarged extensions of the subendocardial plexus and the surviving zones of subepicardial muscle from extensions of subepicardial vessels. The scar often contains depositions of calcium

Discussion

The presence of frequent interarterial anastomoses in the subendocardial layers of the left ventricle in the normal heart has been recognized by a number of observers, including Spalteholz,[7] Gross [8] and more recently Fulton [9,10] In spite of this, little attention had been paid to this arrangement of vessels until Fulton's recent publications Our observations agree very closely with those of Fulton the only sig



Fig. 3 Radiograph of the left ventricular free wall from a 50-year-old man with hypertension and coronary artery disease. The epicardium is to the right. There was extensive fibrosis in the interventricular septum but no lesions in the region from which this section was taken. Note that the Class B vessels, which are small and delicate in their intramyocardial course enlarge as they approach the subendocardial region. (Enlarged X1.5)

nificant discrepancy being that we are unable to correlate enlargement of the subendocardial plexus with coronary artery disease alone. Very large vessels, up to 1,000 microns, are indeed seen in hearts with coronary disease but vessels of similar size are also seen occasionally in hearts from young individuals without coronary disease.

The most striking feature of the Class B vessels which feed the subendocardial plexus is their large caliber and the fact that they fail to taper as they approach the subendocardium. In fact, they are often seen to enlarge substantially as they approach the endocardium. This enlargement usually occurs at the level of the traveculae carneae. It is possible that the enlargement is a result of the lack of an intraventricular counterpressure at the time of the injection.

The presence of such a rich precapillary anastomotic network fits well with Gregg's observation[11] that, when a coronary artery is acutely ligated in a normal dog and the artery is severed distal to the ligature, the blood flowing retrograde from the severed distal branch is bright red and has the



Fig. 4. Radiograph of a section of left ventricular wall from a 65-year-old man with advanced coronary artery disease and an old myocardial infarct, who died of congestive failure. The epicardial surface is to the right. This section is through the base of a papillary muscle, which is at the upper left. There is a dense overgrowth and an interruption of the regular arrangement of Class A vessels in the center of the section, extending into the base of the papillary muscle. The subendocardial plexus is of large size, some vessels reaching 500 microns in diameter. Class B vessels can be seen to traverse the area of overgrowth without interruption. (Enlarged ×3.5)

same oxygen content as blood in the systemic arteries. He also measured retrograde flow during clamping of other coronary arteries, and found that these vessels are the source of such flow. This observation indicates, by another technique, that the coronary bed has a precapillary anastomotic bed similar to that in the head and the limb.

A subendocardial network such as that described above would obviously provide a potential source of collateral blood flow in obliterative disease of the coronary vessels. Such a role has been suggested by Fulton.[9] In such cases the collateral flow to the ischemic area would be dependent on the adequacy of flow to the subendocardial plexus as a whole.

As with any perfused area the flow of blood to the subendocardial plexus as a total unit would be modified by the effective pressure gradient across the transmyocardial course of Class B vessels. This gradient which varies throughout the cardiac cycle could be reduced (thus reducing flow to the subendocardial plexus) by (a) a decreased pressure within the coronary vessels on the epicardial surface (b) an increased myocardial tension tending to collapse the Class B vessels or (c) an increased intraventricular pressure acting at the inner surface of the ventricular wall. In the normal heart these factors seem to be operating to produce a maximum reserve since coronary flow occurs in diastole when myocardial counterpressure and ventricular cavity pressure are minimal and when perfusion pressure is relatively high. Under usual conditions, an adverse change in any one of these factors would be expected to produce little effect. In coronary artery disease when collateral flow to an area distal to the large vessel occlusion is of critical importance and in other special circumstances, these factors may be more important.

It is our belief that the paradoxes of coronary disease may seem to be so only because of our failure to appreciate the existence of the subendocardial plexus as a source of collateral blood flow and the dynamic nature of the gradient across the myocardial course of the Class B vessels.



Fig. 5. Photomicrograph (X76) from the area of myocardium containing the dense overgrowth of small vessels seen in Fig. 4. The homogeneous material filling the vessels is the barium-gelatin injection mass. There is extensive fibrosis through which are scattered islands of intact muscle cells.



Fig 4 Radiograph of a section of left ventricular wall from a 70-year-old man with extensive coronary artery disease and an old anterolateral myocardial infarct, who died of a new posterior infarct. The epicardial surface is to the right. The section is through the anterolateral papillary muscle in a region extensively involved in scar formation and ventricular thinning as a result of the old infarct. In the upper portion there is complete disruption of both Class A and Class B vessels. Subendocardial vessels can be seen entering the area from above, and from the papillary muscle area below. The scattered dense areas are depositions of calcium in the scar (Enlarged ×3)



Fig. 7. Photomicrograph (×34) from an area in the upper portion of the same ventricular wall pictured in Fig. 6. The endocardium is seen to the left. In the subendocardial area, a band of intact muscle cells is seen, beneath which is an area of dense fibrosis. To the right are scattered islands of intact muscle cells.

that are its source. A drop in blood pressure, either primary or induced by an arrhythmia, a rise in heart rate, reducing the diastolic period available for flow, an excessive inotropic response to emotional stress, a rise in end-diastolic pressure in the ventricular chamber: these are all examples of conditions which might adversely affect collateral flow and thus interfere with a strict quantitative relationship between anatomic lesions and clinical symptoms. Similar factors could explain the day-to-day variability in symptoms.

In short, a patient with a given anatomic lesion might manage well until other stresses place excessive demands on a previously adequate collateral network through the subendocardium. Depending on the severity and duration of these stresses, acute symptoms could result with no precipitating anatomic change.

The lamellar localization of myocardial infarction can also be explained by the above-mentioned concepts. A generalized failure of the coronary bed to supply adequate flow to the subendocardial layers and the subendocardial plexus would be expected to cause a subendocardial localization of the ischemia and/or infarction. This fits well with the occasional occurrence of subendocardial infarction in prolonged shock, especially when combined with hypertrophy. Such a mechanism has been suggested by Levine.[13] On the other hand, under conditions of an obstruction to flow to a specific area, in which collateral flow has been largely supplied via the subendocardial plexus, sudden failure of the subendocardial plexus to furnish adequate flow might result in ischemia and/or infarction in the middle third of the myocardium, the area most distant from both endocardial and epicardial sources of supply.

A number of puzzling clinical states involving coronary insufficiency and subendocardial necrosis and infarction are well explained by these concepts. In patients with aortic outflow obstruction, the prolonged and higher pressured isometric contraction phase and the resultant increased myocardial counterpressure, plus a lowered coronary perfusion pressure, might explain the presence of angina in the absence of significant coronary disease. The angina of aortic insufficiency could

result from decreased coronary perfusion pressure plus episodes of elevated end diastolic pressure, both leading to a decreased transmyocardial gradient during diastole. The occurrence of superficial subendocardial hemorrhages and necrosis in hemorrhagic shock in otherwise normal hearts can be explained by the combination of a lowered coronary perfusion pressure plus an increased inotropic activity in response to sympathetic stimulation. The importance of the latter is emphasized by recent studies in this laboratory[12] showing that these lesions can be averted in the laboratory animal by beta sympathetic blockade even when the heart is paced at a rate of 180 beats per minute at a shock level blood pressure.

Additional observations relevant to the possible role of myocardial counterpressure in diminishing myocardial flow are those of Sabiston[14] demonstrating that contraction impedes coronary flow and our observation[15] that, in the tightly contracted hearts of dogs dying of calcium excess, a standard injection fails to fill the subendocardial plexus.

Summary

Postmortem injection studies of the left ventricular wall in 58 human hearts have revealed a characteristic distribution of vessels: those which divide quickly (Class A) and those which penetrate to the subendocardial layers, forming multiple anastomosing arcades (Class B). This subendocardial plexus appears to play an important role as a collateral channel in coronary disease. These anatomic features suggest an explanation for certain features observed in patients with coronary artery disease. This concept assigns a permissive role to the large occlusive lesions of the coronary arteries. Such lesions make the potentially ischemic focus distal to the occlusion dependent on collateral flow through the subendocardial plexus, thus permitting dynamic factors that modify this collateral circulation to become critically significant.

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Chemical composition of the aorta, coronary and cerebral arteries of Europeans and Bantu

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Various workers have compared the arteries of European and Bantu subjects in South Africa and noticed significant differences in the degree of atherosclerosis developed by the two ethnic groups.[1-4] Most of these studies were carried out on the aorta and coronary arteries. Meyer and associates[4] compared the aortas and coronary and cerebral arteries of European and Bantu subjects by the macroscopic method of Gore and Tejada.[7] They found statistically significant racial differences in the onset progress and severity of atherosclerosis in the aortas and coronary arteries, but not in the cerebral arteries. None of the previous studies except that of Anderson and associates,[4] has included chemical analysis of the blood vessels. The chemical studies of these authors were made only on the aortas of adult subjects, and since the composition of the aorta need not necessarily reflect the condition of the smaller arteries, it was decided to follow up the macroscopic study of the aorta coronary and cerebral arteries previously reported[4] by chemical analysis of these vessels. This paper reports the outcome of the chemical analyses.

Material and methods

The aortas and coronary and cerebral arteries of 156 white European and 280 Bantu inpatients who died of natural causes in the Pretoria General Hospital were collected as previously described.[4] The aortas and coronary arteries were almost invariably surrounded by a very well developed layer of fat which was absent in the case of the cerebral arteries. The adventitial layer of the aorta and coronary arteries and where possible also of the cerebral arteries was stripped. In spite of the most painstaking efforts it was not possible to be sure that the adventitial tissue had been completely removed but the same procedure was rigidly applied in every case.

Atherosclerotic index. The degree of atherosclerosis was determined by the atherosclerotic index method of Gore and Tejada.[7]

Absolute dry material. After grading the

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aortas were cut up into small pieces about 0.5 cm. square and dried to constant weight in a vacuum desiccator over concentrated sulfuric acid This procedure which took from 24 to 36 hours, removed about 95 per cent of the moisture. The vacuum-dried material was then ground in a Wiley mill fitted with a 20-mesh sieve and stored at −2°C. in sealed glass containers if not analyzed immediately The coronary and cerebral arteries were dried in like manner except that in the majority of cases it was unnecessary to cut up the vessels into small pieces. To remove the 5 per cent of moisture remaining after vacuum dehydration, the material was exposed to a temperature of 50°C. until the weight remained stable. It was then labeled the *absolute dry material*

Ash and calcium For chemical analysis, 0 1 to 0.2 Gm. of the absolute dry material was ashed at 600°C. for 5 hours, and any remaining organic material was oxidized with nitric acid. The cooled sample was weighed and the calcium concentration determined by a micro-ceric method based on Vogel's macromethod [8]

Total lipids Total lipids were determined on 0 4 to 0.5 Gm of the absolute dry material according to the method of Böttcher[9] and calculated as a percentage of the absolute dry material The extracted lipid was then dissolved in chloroform made up to volume and aliquots used for the determination of cholesterol phospholipids, and triglycerides.

Cholesterol Total cholesterol was determined by the method of Zlatkis and associates[10] as modified by Rosenthal and associates,[11] and free cholesterol was determined by the method of Zak and associates.[12]

Phospholipids The method of Brown[13] was employed for phospholipid studies.

Triglycerides The method used for the determination of triglycerides was based on the determination of glyceride-glycerol Triglycerides and cholesterol were separated chromatographically from phospholipids on a silicic acid column [14-16] After saponification the glycerol was oxidized to formaldehyde which gives a red color with chromotropic acid [14,17,18] The difficulty in getting duplicate results with column separation reported by Randup[19] was not encountered in the present study Each blood vessel was analyzed separately except in the age group 0-9 years in which the dry material of the individual vessels was insufficient for complete analysis and had to be pooled

Results

The mean values for the different constituents studied in the aorta and the coronary and cerebral arteries are presented in Tables I II and III

Since the correlation coefficient r does not take the effect of sample size into account, it was decided to test whether the correlations between the various vessel constituents differed significantly from zero by calculating the transformed and standardized values (t) of the correlation coefficients according to the method described by Kenney and Keeping [19] The age group 0-9 years was not included in this statistical analysis. A value of t greater than 2.33 or smaller than −2.33 was considered to be significant. A 2 per cent level of significance (2.33) was chosen because of the great number of comparisons between dependent quantities that had to be made.

The normalized values (t^1) of the test statistic testing for differences between the mean values of the different vessel constituents in the different age and sex groups of the two races were analyzed by the method described by Kenney and Keeping [19b] As in the first method (*vide supra*) a t^1 value greater than 2 33 or smaller than −2.33 was considered to be significant. A positive value for t^1 indicated a greater mean value for white subjects than for Bantu subjects and a negative value, a greater mean value for Bantu subjects.

Age The usual trend shown by the mean concentrations (Tables I III) of the different chemical constituents was an initial decrease followed by a progressive increase with increasing age. From the age of 9 to 70 years the concentration of the different constituents showed statistically significant positive correlations with age

SEX. Sex related differences in the chemical composition of the arteries were present in white subjects in the fourth decade only In Bantu subjects, slight differences be-

Table I Mean values for various constituents of the aorta (expressed as gram per cent of the

Age (yr.)	Number of cases	Index	Ash	Calcium	Total lipids
0–½	W ♂+♀ 29	0	2 860	075	3 745
	B ♂+♀ 61	0	2 481	092	3 780
½–2	W ♂+♀ 10	0	1 691	070	2 606
	B ♂+♀ 34	0	1 700	072	2 588
2–9	W ♂+♀ 10	0	1 740	057	2 889
	B ♂+♀ 24	0	1 662	058	2 867
0–9	W ♂+♀ 49	0	2 393	070	3 338
	B ♂+♀ 122	0	2 104	080	3 260
10–19	W ♂ 3	139	2 340	078	3 530
	W ♀ 2	064	2 300	065	3 655
	B ♂ 10	061	2 277	073	3 581
	B ♀ 13	097	2 179	079	3 689
20–29	W ♂ 6	320	2 977	122	5 718
	B ♀ 20	085	2 938	201	5 015
30–39	W ♂ 15	1 151	3 527	469	7 322
	W ♀ 9	958	3 219	321	5 580
	B ♂ 19	738	5 055	417	5 818
	B ♀ 20	525	2 958	312	5 936
40–49	W ♂ 19	9 120	6 818	1 809	10 789
	W ♀ 11	3 083	3 995	713	7 573
	B ♂ 21	2 926	3 219	529	7 059
	B ♀ 14	1 701	3 454	537	7 078
50–59	W ♂ 19	13 124	8 765	2 488	13 667
	W ♀ 10	9 587	5 790	1 373	11 992
	B ♂ 19	3 872	4 786	918	8 577
	B ♀ 10	1 831	5 550	1 181	7 741
60–69	W ♂ 13	20 443	10 888	3 405	16 392
	B ♀ 12	10 030	8 588	2 414	9 993

W White subject B Bantu subject

tween the sexes were present throughout (Tables I III)

RACE. Racial differences were present in the aortas and coronary arteries of males from the third decade onward increasing with age Slight racial differences were present in the aortas and coronary arteries of females, and in the cerebral arteries of both sexes (Tables I III)

Atherosclerotic indices

AGE. The mean atherosclerotic indices increased throughout with increasing age. Beyond the second decade the increase was faster in the aortas and even more so in the coronary arteries of white males (Tables I III) In general the increases were statistically significant

SEX The mean atherosclerotic indices of the aortas and coronary arteries of adult white subjects showed considerable sex differences. Sex differences in the cerebral arteries of white subjects and in the aortas and coronary and cerebral arteries of Bantu subjects, however were slight (Tables I III)

RACE. The mean atherosclerotic indices of the aortas and coronary arteries of European and Bantu subjects differed considerably (Tables I III) These racial differences were statistically significant beyond the fifth decade in males and beyond the sixth decade in females. The cerebral arteries did not show significant racial differences

Ash

AGE. The mean ash concentration of the three vessels decreased initially but thereafter increased progressively The aortas of both races and the coronaries of white males regained their initial values in the third decade The coronaries of Bantu subjects regained their initial ash concentration much later The cerebral arteries failed to recover their initial values (Tables

absolute dry material)

Total cholesterol	*Free cholesterol*	*Ester cholesterol*	*Phospholipids*	*Triglycerides*
618	385	232	1 635	456
639	394	245	1 646	462
398	269	129	1 109	314
382	264	119	1 054	309
446	274	172	1 118	357
433	300	133	1 173	334
538	339	199	1 422	407
527	339	188	1 388	394
699	366	333	1 312	413
677	343	334	1 454	428
688	352	335	1 371	389
710	358	352	1 390	386
1 448	682	766	1 872	621
1 241	646	595	1 760	466
2 452	1 042	1 410	2 322	790
1 568	706	862	1 977	531
1 762	874	888	2 073	530
1 483	761	722	1 938	534
4 349	1 807	2 542	2 844	1 104
2 612	1 085	1 527	2 353	666
2 412	1 088	1 324	2 275	585
2 322	1 051	1 271	2 145	598
6 057	2 692	3 364	3 308	1 110
4 796	1 850	2 946	2 843	982
3 111	1 363	1 748	2 549	678
2 603	1 173	1 430	2 256	635
7 835	3 419	4 416	3 491	1 180
4 165	1 781	2 384	2 719	709

I III) The ash content of the aortas and coronary arteries showed a statistically significant positive correlation with age and atherosclerotic index. Marked differences between the mean ash concentrations of the aortas and of the coronary arteries of Europeans were present only in older subjects. The cerebral arteries had the highest mean ash concentration of the three vessels during the first 6 months of life but this value increased very slowly with increasing age and was soon overtaken by the corresponding values for the other arteries. In Bantu the ash concentrations of the three types of vessels differed very little from one another at different ages.

SEX. Only the aortas and coronary arteries of white adult subjects showed significant sex-related differences in the mean ash concentrations.

RACE. The mean ash concentrations of corresponding vessels differed in European and Bantu infants (Tables I III) but only in the aortas and in the coronary arteries of older European and Bantu subjects were the differences statistically significant

Calcium

AGE. Only the aortas showed some initial decrease in mean calcium concentration (Tables I III) For the rest a statistically significant positive correlation was present between age, atherosclerotic index ash concentration and calcium concentration Aortas almost invariably had higher calcium concentrations than did coronary or cerebral arteries. In white subjects up to the age of about 30 years the calcium concentrations of the coronary and cerebral arteries differed very little but beyond this age higher concentrations were found in the coronary arteries. In Bantu the calcium concentrations of coronary and cerebral arteries differed very little from one another at different ages

Table II Mean values for various constituents of the coronary arteries (expressed as gram per

Age (yr)	Number of cases		Index	Ash	Calcium	Total lipids
0–½	W ♂+♀	31	0	2 757	035	6 032
	B ♂+♀	66	0	2 447	042	5 941
½–2	W ♂+♀	10	0	1 706	047	6 306
	B ♂+♀	34	0	1 621	046	5 733
2–9	W ♂+♀	10	0	2 261	047	6 700
	B +♀	24	0	1 780	054	5 780
0–9	W ♂+♀	51	0	2 454	040	6 021
	B ♂+♀	124	0	2 091	046	5 853
10–19	W ♂	3	0	2 950	074	7 170
	W ♀	2	0	1 690	059	6 720
	B ♂	10	0	1 978	056	6 826
	B ♀	13	002	2 423	102	6 511
20–29	W ♂	6	818	2 335	154	11 762
	B ♀	20	097	2 263	064	7 710
30–39	W ♂	15	2 103	3 030	338	12 144
	W ♀	9	075	1 883	095	9 250
	B ♂	18	630	2 389	128	9 840
	B ♀	19	138	1 865	083	8 350
40–49	W ♂	13	8 732	6 330	1 577	18 055
	W ♀	10	3 137	3 308	416	12 040
	B ♂	18	1 112	2 189	132	10 192
	B ♀	14	293	1 983	118	9 530
50–59	W ♂	16	11 428	8 761	2 579	16 183
	W ♀	10	9 918	4 543	844	16 880
	B ♂	18	1 240	2 252	251	11 880
	B ♀	10	2 454	2 667	162	12 284
60–69	W ♂	10	22 330	20 669	7 258	14 075
	B ♀	12	7 957	5 265	1 383	12 146

W White subjects, B Bantu subjects

SEX The mean calcium concentrations in the aortas and coronary arteries of older white males differed very considerably from those of the corresponding females.

RACE. Racial differences in the mean calcium concentrations of the three arteries in infants and children were slight (Tables I III) Beyond the age of 20 years calcium increased much faster in the aortas and coronaries of white males than in those of Bantu males (Tables I and II) the differences eventually becoming statistically significant Beyond the age of 40 years, the coronaries of females showed similar racial differences. Differences between the cerebral arteries of the two races were slight and not significant (Table III)

Total lipids

AGE. Except in the coronaries of white subjects the mean total lipid concentrations decreased initially (Tables I III) The high initial values were regained in the second or third decade and the figures continued to rise with increasing age This positive correlation with age was statistically significant in all three arteries of the two races. With few exceptions, notably the calcium in the coronaries of white males significant positive correlations were obtained between total lipids, atherosclerotic index, and calcium concentration Up to the age of 9 years the mean total lipid concentration in the aortas was about half that in the coronary and cerebral arteries. With increasing age the increment in mean total lipid was greatest in the coronaries and then in the aortas Beyond the fifth decade the total lipid concentrations in the aortas and coronary arteries approached each other and exceeded that in the cerebral arteries very considerably Changes in the total lipid of the cerebral arteries were comparatively slight (Tables I III) Böttcher and associates[19] almost

cent of the absolute dry material)

Total cholesterol	Free cholesterol	Ester cholesterol	Phospholipids	Triglycerides
739	501	238	1 634	2 724
756	496	260	1 874	2 453
742	477	266	1 612	2 989
629	318	311	1 500	2 667
659	403	256	1 392	2 699
645	363	282	1 497	2 733
724	477	247	1 582	2 771
700	421	278	1 699	2 566
994	526	468	1 616	3 352
791	398	394	1 831	3 039
854	442	412	1 560	3 062
802	405	397	1 533	3 086
2 945	1 162	1 783	2 533	3 816
1 012	516	496	1 712	3 413
3 197	1 257	1 940	2 606	3 920
1 588	677	911	2 084	3 849
1 684	690	994	1 913	4 240
1 269	494	775	1 763	3 754
6 603	2 932	3 671	3 154	4 704
2 901	1 053	1 848	2 307	4 246
1 786	654	1 314	2 044	4 370
1 721	623	1 098	1 854	4 150
5 296	2 639	2 657	2 942	4 570
4 949	1 775	3 174	2 817	5 100
2 476	1 008	1 468	2 121	4 678
2 862	1 042	1 820	2 139	4 760
4 422	1 960	2 462	2 464	4 295
2 694	1 061	1 633	2 037	4 732

invariably found that the lowest total lipid concentrations were present in the aortas

SEX. The aortas of older white males contained more lipid than the corresponding vessels of white females, and this sex related difference was even more marked in the coronaries. Sex differences were slight in the cerebral arteries of white subjects, and in all of the vessels of the Bantu (Tables I III)

RACE. Racial differences in mean total lipid concentration were slight during the first 6 months, but increased with increasing age, especially in males (Tables I III) The differences eventually became statistically significant. The coronary arteries of females and the cerebral arteries of males and females showed no statistically significant racial differences.

Cholesterol

AGE. After an initial decrease (Tables I III) the mean concentrations of total free and ester cholesterol showed a statistically significant positive correlation with age Significant positive correlations were also present between these three constituents and the atherosclerotic index, calcium concentration and total lipid concentration The coronary arteries of white males did not show this correlation between cholesterol and calcium

The mean concentration of free cholesterol exceeded that of ester cholesterol in the aortas and coronary arteries of white subjects until the third decade and in Bantu subjects until the fourth decade Beyond these ages, ester cholesterol exceeded free cholesterol (Tables I and II) Thus both free and ester cholesterol increased with increasing age and hence with increasing severity of atherosclerosis, but the percentage of the total cholesterol which esterified also rose steeply with increasing severity of atherosclerosis. In the

Table III Mean values for various constituents of the cerebral arteries (expressed as gram per

Age (yr)		Number of cases	Index	Ash	Calcium	Total lipids
0–½	W ♂ + ♀	18	0	3 404	056	6 550
	B ♂ + ♀	53	0	2 590	049	6 375
½–2	W ♂ + ♀	9	0	2 281	064	5 008
	B ♂ + ♀	31	0	2 735	051	5 085
2–9	W ♂ + ♀	9	0	3 074	077	4 970
	B ♂ + ♀	2	0	2 570	056	4 811
0–9	W ♂ + ♀	36	0	3 041	063	5 769
	B ♂ + ♀	106	0	2 628	051	5 673
10–19	W ♂	3	0	2 300	076	5 010
	W ♀		0	1 900	064	4 970
	B ♂	10	0	2 608	090	5 090
	B ♀	13	0	2 734	102	5 303
20–29	W ♂	5	006	2 654	084	5 196
	B ♀	20	001	2 818	132	5 295
30–39	W ♂	9	062	2 871	159	6 160
	W ♀	8	015	2 429	161	5 226
	B ♂	18	366	2 292	148	5 647
	B ♀	19	391	2 206	137	6 236
40–49	W ♂	12	313	2 546	156	7 568
	W ♀	10	031	2 644	157	5 639
	B ♂	18	443	2 131	158	6 158
	B ♀	14	605	2 138	166	6 261
50–59	W ♂	16	682	2 419	246	7 761
	W ♀	8	1 084	2 881	205	9 374
	B ♂	18	796	1 944	167	6 667
	B ♀	8	391	2 [illegible]	238	6 573
60–69	W ♂	10	1 953	2 625	2 3	8 3 0
	B ♂	13	2 107	2 332	278	6 672

W White subjects. B Bantu subjects.

cerebral arteries free cholesterol exceeded ester cholesterol from birth until [illegible]0 years of age (Tables I III) confirming that a lower atherosclerotic index is associated with a slower rate of esterification In both races the cerebral arteries had the highest, and the aortas the lowest, free and ester cholesterol concentrations during the first 6 months of life. In white subjects the increment in cholesterol with age was greater in the coronary arteries and next greatest in the aortas By the third decade the concentration in the coronaries was about double that in the aortas or cerebral arteries Beyond the fifth decade, differences in mean cholesterol concentrations in the aortas and coronaries were slight (Tables I III) In Bantu increments in cholesterol tended to be greatest in the aortas.

SEX In adult Europeans the mean concentrations of total free and ester cholesterol were considerably higher in the aortas and coronary arteries of males than of females The differences reached a maximum in the 40-to-49 year age group Thereafter the sex differences tended to become narrow again Sex-related differences in the cerebral arteries of Europeans were slight. In the Bantu sex differences were slight for all three arteries (Tables I III)

RACE. Racial differences in the mean concentrations of free and ester cholesterol were not present during the first 6 months of life. With increasing age cholesterol increased more rapidly in the aortas and coronary arteries of white than of Bantu subjects (Tables I III) These racial differences eventually became statistically significant.

Phospholipids

AGE. Like the cholesterol concentration the mean phospholipid concentration cal-

cent of the absolute dry material)

Total cholesterol	*Free cholesterol*	*Ester cholesterol*	*Phospholipids*	*Triglycerides*
1 194	804	389	3 076	995
1 153	24	429	2 825	376
919	635	284	2 380	346
963	651	311	2 162	306
833	569	264	2 321	338
858	586	272	061	296
1 035	703	33?	713	369
1 036	674	362	2 472	339
853	520	333	2 330	346
852	576	2 6	2 321	338
826	476	349	2 069	313
901	500	401	2 128	325
911	545	363	2 363	381
867	489	378	2 134	333
1 140	650	490	2 505	489
966	557	409	2 431	391
1 020	580	440	2 223	392
1 123	589	534	315	400
1 634	916	717	2 686	596
1 057	620	437	413	421
1 404	753	651	2 319	413
1 248	600	648	2 321	413
1 730	962	768	2 657	664
2 234	1 098	1 136	2 649	1 286
1 362	83[illegible]	730	2 403	447
1 444	737	707	2 388	447
2 487	1 374	1 113	857	632
1 644	906	738	2 433	424

culated as a percentage of the absolute dry material decreased initially but thereafter increased very gradually with increasing age (Tables I III) Except in the case of the coronary arteries of whites this positive correlation with age was statistically significant Significant correlations were also present between phospholipids, atherosclerotic index, total lipids, and the cholesterol fractions. During the first 6 months of life the cerebral arteries contained the highest phospholipid concentration The rate of increase in phospholipid with increasing age was slight in comparison with that of the other lipid fractions.

SEX. In general the differences in the mean phospholipid concentrations resembled those found for cholesterol (Tables I III)

RACE. Racial differences in phospholipid concentration were absent during the first 6 months of life However with increasing age phospholipid increased more rapidly in the aortas and coronary arteries of white than of Bantu subjects (Tables I and II) and the differences eventually became statistically significant

Triglycerides

AGE. Like most of the other constituents mean triglyceride also decreased initially before starting to increase (Tables I III) The positive correlation with age was statistically significant except in the case of the coronary arteries of white males and in the cerebral arteries of both races With few exceptions significant positive correlations were found between triglyceride and atherosclerotic index, calcium and the various lipid fractions. The coronary arteries of both races contained much more triglyceride than did the aortas or cerebral arteries. These differences in the vessels were present from birth to 70 years of age (or onward)

SEX The mean triglyceride concentrations showed the same sex trends as were found for the other lipids, except that sex differences were only slight in the coronary arteries (Tables I III)

RACE Racial differences were slight during the first 6 months of life but developed and increased with increasing age (Tables I III) Only in the aortas were these differences statistically significant

LIPID FRACTIONS CALCULATED AS PERCENTAGE OF THE TOTAL LIPID The mean concentrations of the different lipid fractions presented in Tables I III were calculated as percentages of the absolute dry material The different lipid fractions were also calculated as percentages of the total lipid and tested statistically for correlations with age and the other vessel constituents Calculated in this way the free cholesterol and ester cholesterol once again showed statistically significant positive correlations with age atherosclerotic index, calcium and total lipid but statistically significant negative correlations with phospholipids and triglycerides.

Discussion

Several aspects of the present findings deserve special notice These include (a) the quantitative chemical changes in the arteries during the first decade (b) the quantitative differences in the chemical composition of the different vascular beds of the newborn child (c) the increase with increasing age in the quantitative chemical differences between the different vascular beds (d) the presence of quantitative sex related chemical differences in the aortas and coronary arteries of older white subjects, and their absence in the cerebral arteries of whites and all three arteries of Bantu subjects (e) the absence of noteworthy quantitative differences in the chemical composition of corresponding vessels of the two races during the first 6 months of life and (f) the subsequent development of such differences and their progressive increase with increasing age.

According to Moulton [21] the mammalian body shows a rapid decrease in water content and an increase in protein and ash content from birth onward until chemical maturity is reached He also states that the most striking change in the chemical composition of the mammalian body that occurs with growth and development is an increase in fat content Moulton based his views on an analysis of the fat free tissues of the mammalian body Weisberg[22] and Morison[23] have emphasized the high water content of the body of infants At the same time the blood plasma of babies has been stated to contain higher concentrations of sodium potassium phosphorous sulfur organic acids, and proteinate than that of subjects 5 to 20 years old [23] Lansing[24] analyzed the medias of human aortas and found higher elastin and calcium concentrations in the 0-10-year age group than in the 11 20-year age group No satisfactory explanation emerges from these observations for the initial decrease in the concentration of the various constituents found in the present study However the high water content of the newborn child and its gradual decrease with increasing age must be an important contributory factor

The aorta and the coronary and cerebral arteries differ in histologic structure[25] and in quantitative chemical composition [26] In the present study chemical differences were already found at birth In certain vascular beds these chemical differences tended to increase with increasing age, whereas in others they tended to decrease Quantitative chemical differences between corresponding vessels of white and Bantu subjects were negligible or absent at birth but very considerable differences developed in the aortas and in the coronary arteries.

The question arises whether the intrinsic structural and chemical differences between different arterial beds dictate the time of onset and control the progress of atherosclerosis. This seems to be unlikely for the histologic structure and chemical composition of corresponding vessels of newborn white and Bantu subjects are apparently identical yet the time of onset and rate of progress of atherosclerosis in the aortas and coronary arteries of the two races differ widely

The structural and chemical differences between the vascular beds should be regarded as genetically determined characteristics related to anatomic organization and functional requirement and unlikely to predispose to atherosclerosis. The pro-

cesses concerned in the development of the progressive chemical changes are those associated with aging and atherogenesis. Very generally speaking aging may be regarded as a genetically determined function which will affect all vascular beds, although perhaps not simultaneously Atherogenesis, on the other hand is a secondary process selective in its anatomic situation and in its rate of progress. It is secondary in the sense that it is preceded by aging of the vessel wall or by chemical derangements in the blood precipitated by one or more of a multitude of factors, including physical activity or inactivity endocrine activity diet and hemocoagulation It is selective in the sense that arteries which are subjected to greater mechanical stress and strain such as the aorta with its forceful rhythmic stretching and the coronaries with their rhythmic flexion are affected earlier and also more severely than such vessels as the cerebral arteries, which function under less demanding mechanical conditions. The mechanical part of the atherosclerotic process is common to white and Bantu subjects alike, but the humoral or chemical aspects differ and atherosclerosis is the result of an interplay between mechanical and humoral (chemical) forces. In all three of the vessels of the Bantu and in the cerebral arteries of Europeans, atherosclerosis must apparently as a rule, be preceded by aging whereas in the aorta and coronary arteries of Europeans, atherosclerosis appears to result more often from intraluminal chemical derangements superimposed upon mechanically strained arteries.

Summary

The aortas and the coronary arteries and cerebral arteries of 156 white European and 280 Bantu subjects were analyzed for their ash calcium total lipid free and ester cholesterol phospholipid and triglyceride concentrations.

At birth the various arteries differed considerably from one another in quantitative chemical composition These differences increased with increasing age due in part to selective onset and progress of atherosclerosis. The general trend with age was an initial decrease in the mean concentrations of the various chemical constituents followed by a progressive increase

Quantitative chemical differences between corresponding arteries of European and Bantu infants were slight during the first 6 months of life

Chemical changes associated with atherogenesis developed earlier and progressed faster in the aortas and coronary arteries of Europeans than in the corresponding arteries of Bantu These differences were not present in the cerebral arteries.

The chemical analysis of the arteries confirmed the earlier conclusions reached by Meyer and associates.[6]

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Determination of renal blood flow by single injection of Hippuran I^{131} in man

A comparison with the standard clearance technique

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A reliable yet easily performed test to measure renal blood flow would be of great clinical value. The previously accepted method of PAH clearance although accurate, is laborious. Sapirstein and associates[1] proposed a single injection technique to determine the renal clearance of a specific substance by use of a two-compartment analysis. Gott and associates,[2] believing that a one-compartment system more nearly fit their data compared the clearance by single injection of Hippuran I^{131} with that of the classic PAH technique. Since average deviation between the two was no greater than 8 per cent in 8 patients, they suggested that this was a useful accurate clinical method for measuring renal blood flow. Recently[3] the accuracy of the single injection method of this same substance in dogs has been shown to agree well with directly measured kidney blood flows. In 21 experiments in 11 dogs the average deviation of these two methods was 7.6 per cent. In some of these dogs, standard clearances were calculated by the technique of constant infusion, renal A-V differences and urine collections. The correlation with directly measured flows was again excellent and the conclusion reached was that clearance of I^{131} Hippuran is suitable for determining renal flow. The purpose of this study is to confirm the reliability of the single injection technique as compared with standard clearance techniques in human subjects and to report renal extraction ratios of I^{131} Hippuran.

Methods

Patients of both sexes, varying in age from 20 to 60 years, were selected from the medical hospital wards. Both history and physical examination disclosed no evidence of renal disease. In addition the urinalysis and blood urea nitrogen were normal. Standard urea or creatinine clearances were not performed.

The patients were premedicated with 50 to 75 mg. of meperidine. The studies were performed in the early afternoon rather than under standard basal conditions.

1. Single injection method. An intravenous infusion of 5 per cent dextrose in

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water was started in the left arm. A No. 14 Foley catheter was inserted into the bladder under sterile conditions. A polyethylene catheter was introduced percutaneously into the right femoral vein and positioned in the inferior vena cava well below the renal veins. I^{131} Hippuran in doses of 40 to 100 μc was given as a single injection through the intravenous tubing. Samples of venous blood from the catheter in the inferior cava were obtained at 11, 14, 17, and 20 minutes after the injection.

2. Standard clearance technique. Immediately after completion of the single injection study, 250 ml. of 5 per cent dextrose in water containing 50 to 120 μc of Hippuran I^{131} was administered intravenously at a constant rate of 5 ml. per minute. Under fluoroscopic control the polyethylene catheter in the inferior cava was then advanced into the right renal vein, and a sample of blood was drawn for determination of oxygen content in order to confirm the location. A No. 20 arterial needle was then inserted into the right femoral artery. Ten minutes after the start of the infusion the bladder was emptied, washed with 40 c.c. of saline, and the collection of urine was started. Simultaneous samples from the arterial and renal veins were obtained at the beginning, the middle, and the end of the period of collection of urine, which varied from 16 to 31 minutes. At the end of the clearance period the bladder was washed with 40 c.c. of saline and the wash was added to the urine collected. Samples of blood and urine were counted in an Atomium well scintillation counter. Thus, the results of the single-injection experiment using I^{131} Hippuran were compared with those of the clearance period of from 15 to 30 minutes which immediately followed.

Calculations

A. Single injection method. The method of calculation and the theory of application have been presented in previous reports from this laboratory.[2,3] A one-compartment system model has been proposed for the clearance of Hippuran I^{131} and the following formulas used:

$$\text{Clearance (RBF)} = mv$$

where m = the slope of the blood concentration curve drawn between 10 and 20 minutes, and v = the volume of distribution from which the tracer is being cleared. This was calculated from the intercept at zero time and the dose injected.

B. Standard clearance method. The formula used was

$$\frac{UV}{B} \times \frac{1}{ER}$$

where UV = total urine activity per minute expressed as counts per milliliter per minute, B = blood activity, counts per milliliter per minute, taken as the average of the three arterial blood samples, and

$$\text{ER (extraction ratio)} = \frac{AB - VB}{AB}$$

where AB and VB represent the activity in arterial and renal vein blood, respectively.

Results

Table I gives the results of the two methods in which the single injection technique was compared with the standard clearance method. The average difference was +2.9 per cent, and the average deviation was 5.7 per cent, over a range of blood flow from 520 to 1,495 ml. per minute. Table II gives pertinent data from which all calculations were made.

1. Single injection method. The curves plotted on semilogarithmic paper disclosed three phases as described in a previous report from this laboratory (Fig. 1).[3] The first phase was an early, rapid disap-

Table I

Patient	Standard clearance technique (ml./min.)	Single-injection technique (ml./min.)	Per cent difference
1 R.K.	850	926	+ 8.9
2 C.H.	775	820	+ 5.8
3 J.R.	590	570	− 3.4
4 T.B.	800	700	−12.5
5 S.W.	520	555	+ 6.3
6 L.C.	975	993	+ 1.9
7 B.H.	1,495	1,385	− 7.4
8 M.B.	570	565	− 1.0
9 W.A.	1,130	1,185	+ 4.3

Average difference = +2.9 per cent.
Average deviation = 5.7 per cent.

Table II

Patient	*Standard clearance technique*				*Single-injection technique*	
	Urine activity	*Blood activity*	*U1/B*	*Extraction ratio (%)*	*Dilution volume*	*T½*
R.K.	1 630 000	2 601	630	74 4	17 5	13 10
C.H.	1 450 000	2 474	590	76 2	17 5	14 75
J R.	693 000	2 277	390	66 0	16 25	19 70
T.B	745 000	1 144	650	77 0	11 00	10 90
S.W	760 000	1 952	590	75 2	15 40	19 20
L.C.	707 000	1 100	642	66 0	18 68	13 00
B H.	1 340 000	1 179	1 135	76 0	20 00	11 00
M B.	1 095 600	2 479	442	78 0	13 05	16 00
W.A.	780 000	880	890	78 6	23 45	13 70

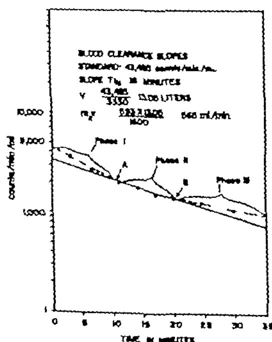


Fig. 1 See text.

pearance curve which ended at about 9 to 11 minutes. The second phase showed a slower single exponential decline lasting from 11 to 20 minutes. After approximately 20 to 22 minutes, the slope deviated from a single exponential and declined in a slower manner (Phase III) Although we are not yet certain what causes the departure from the exponential at this point, it is thought that at very low concentrations a portion of the Hippuran removed into renal cells is not firmly bound and is released or washed out into the venous circulation (our unpublished data and Reference 12) An alternate explanation however is that in order to maintain a single exponential clearance an optimal concentration above that usually seen at this time of the clearance period is required It should be realized that injections of radioactive material require not more than 300 to 500 micrograms of Hippuran At these very low concentrations in the blood firmer binding to plasma proteins may exist. Presently the effect of larger carrier amounts of Hippuran is being studied

The dilution volumes in these subjects varied between 11 and 23 5 liters. This variation seemed to parallel the patient's weight. The half times of the slope of the 10 to 20-minute phase were between 10 25 and 16 minutes. The calculated renal blood flow varied between 555 and 1 385 ml per minute (Table I)

2 *Standard clearance method* The flow of urine varied between 0 6 and 6 ml per minute. The arterial level of Hippuran I^{131} remained fairly stable during the period of infusion The extraction ratios varied between 0 66 and 0 78 with a median of 0 72 ± 0 06 and a mean of 0 735 (Table II) The extraction ratio remained constant in each individual case In a few isolated samples it was apparent that a single extraction ratio was

water was started in the left arm. A No. 14 Foley catheter was inserted into the bladder under sterile conditions. A polyethylene catheter was introduced percutaneously into the right femoral vein and positioned in the inferior vena cava well below the renal veins. I^{131} Hippuran in doses of 40 to 100 μc was given as a single injection through the intravenous tubing. Samples of venous blood from the catheter in the inferior cava were obtained at 11, 14, 17 and 20 minutes after the injection.

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Calculations

A. *Single injection method.* The method of calculation and the theory of application have been presented in previous reports from this laboratory.[1,3] A one-compartment system model has been proposed for the clearance of Hippuran I^{131} and the following formulas used:

Clearance (RBF) = mv

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where UV = total urine activity per minute expressed as counts per milliliter per minute, B = blood activity, counts per milliliter per minute, taken as the average of the three arterial blood samples, and

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2 C.H.	775	820	+ 5.8
3 J.R.	590	570	− 3.4
4 T.B.	800	700	−12.5
5 S.W.	520	555	+ 6.3
6 L.C.	975	993	+ 1.9
7 B.H.	1,495	1,385	− 7.4
8 M.B.	570	565	− 1.0
9 W.A.	1,130	1,185	+ 4.3

Average difference = +2.9 per cent.
Average deviation = 5.7 per cent.

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The spatial ventricular gradient during alterations in the ventricular activation pathway

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Few electrocardiographic measurements have attracted as much general interest as the ventricular gradient. Since its original description by Wilson and associates,[1] the literature on the basic concept and its applications has increased enormously The most extensive contributions were made by Ashman and associates[2-4] Bayley[5] and Schaefer and associates[6,7] The ventricular gradient was defined as the net electrical effect of the differences in time course of ventricular depolarization and repolarization Although not a gradient in the physical sense this term has been generally accepted For a single isolated muscle cell the time integral of the depolarization potential equals that of repolarization but both are of opposite sign Since in most body surface ECG leads QRS and T are equal in sign a difference in the time courses of depolarization and repolarization was postulated by Wilson. This difference can be simply obtained by adding the time integrals of QRS and T ($\bar{A}QRS + \bar{A}T = \bar{V}G$)

A further postulate of Wilson and associates[1] was that of the independence of the ventricular gradient of the pathway of cardiac activation A dog's heart was stimulated at 15 different points, and the ventricular gradient was obtained for each of the cardiac cycles which differed in the pathway of activation The results were considered to be close enough to postulate independence of the ventricular gradient from the activation pathway Simonson and associates[8] and Angle[9] were unable however to confirm these area determinations when they re-examined Wilson's original records.

Ashman and associates[3,4] pointed out first that the ventricular gradient hitherto derived from limb leads only represents solely a vector projection onto the frontal plane However such an entity cannot be completely described in a single projection only In order to obtain a more accurate spatial description a front back component needs to be added to the frontal plane leads. Furthermore time integrals need to be obtained from leads with known directions and lead strength The latter attribute is essential for spatial vector construction because significant distortions in magnitude and direction may be introduced by differences in lead strength

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Since ECG leads with a relatively high degree of constancy in lead strength and direction became available through the introduction of corrected orthogonal leads, it appeared to be important to re-examine some of the basic postulates of Wilson Records exhibiting both normal sinus beats and premature ventricular contractions were considered to be adequate for testing the hypothesis of constancy of the ventricular gradient during variations of the ventricular activation pathway

The studies by Simonson and associates[7] and Angle[8] both pointed out the importance of the methods used for obtaining time integrals of the electrocardiogram In the present study these integrals were obtained by digital computation whereby the influence of the thickness of the ECG trace is eliminated. In the analog to-digital data conversion process, voltage values remain at a discrete level without adding an additional source of error introduced in graphic displays. Furthermore the beat to-beat variation was investigated since such variations represent an additional factor which may lead to discrepancies in results from the same record

Material and methods

Electrocardiograms from 71 patients exhibiting both normal sinus beats (NSB) and premature ventricular contractions (PVC) were selected for the study Recordings were made on magnetic analog tape. Subsequently they were digitized at a sampling rate of 1 000 per second as described previously[11] Computer methods used for wave recognition and area integration have also been reported[12] The P wave was included in the time integral of QRS because it is generally assumed that the atrial gradient is zero[6,13] Since part of atrial repolarization potentials are hidden in the QRS complex, omission of the P wave leads to an error in computation U waves, when present, were also included. In the absence of a generally accepted theory on their genesis, they were considered to be part of the repolarization process.

Great care was taken to select complexes without base-line shifts because the latter can distort the magnitude of time integrals considerably Only records with identical levels of the T P segment in successive beats were selected for the study

In order to obtain an estimate of the beat to-beat variability of the ventricular gradient, which is due mainly to respiration time integrals from three consecutive beats were computed in 10 cases. For the heart and respiratory rates encountered a complete respiratory cycle encompassed three to six cardiac cycles. Therefore, three heartbeats covered one transition from inspiration to expiration

For obtaining a true measure of the sum total of the heart's electromotive forces one should have available ECG leads with identical lead strength i e the same ratio between magnitude of recorded potential in each lead and the current strength generated in the heart. The more recently developed corrected orthogonal lead systems[13] represent a first-order approximation to this ideal. Although very similar in performance, these systems cannot be designed to agree completely In order to eliminate any error which might have been introduced by a particular lead design two different corrected lead systems were used in the present study Schmitt's SVEC III[16] and Frank's system[17]

Time integrals of NSB were compared with PVC in records obtained by both lead systems. Tracings from two series of normal subjects were also compared in order to evaluate discrepancies between lead systems. A sample of 76 normal records obtained with the SVEC III system and a larger sample of 510 records obtained with the Frank system[18] were used When amplitude data of the Frank system were multiplied by a constant factor of 1 48[19] values for $S\hat{A}QRS$ (spatial time integral vector of QRS) were almost identical (100 vs. 101 per cent) $S\hat{A}T$ (spatial time integral vector of T) and $SV\hat{G}$ (spatial time integral vector of the ventricular gradient) showed a similarly close relationship (100 vs. 97 per cent and 100 vs. 102 per cent, respectively) Mean differences in azimuth and elevation angles were 11 and 5 degrees.

Results

The ECG interpretation of 71 records used in the study is listed in Table I A typical example of the beat to-beat vari

Table I ECG interpretation of the records used in the study

Normal	12
Left ventricular hypertrophy	11
Right ventricular hypertrophy	4
Left ventricular conduction defect	8
Right ventricular conduction defect	5
Myocardial infarction	23
Nonspecific myocardial changes	7
Ventricular conduction defect unclassified	1
Total	71

Table II Representative example of time integrals of three consecutive cardiac cycles in orthogonal leads X Y and Z

	Orthogonal lead		
	ÂQRST X	ÂQRST Y	ÂQRST Z
First cardiac cycle	−6 1	−46 6	− 8 0
Second cardiac cycle	+2 6	−35 1	−10 6
Third cardiac cycle	+3 3	−37 2	− 5 8

Values indicate μV sec. Note that the changes are most conspicuous when readings are close to zero. The largest absolute change was found in lead Y however.

ability during normal sinus rhythm is given in Table II From these data it becomes obvious that the changes from one cardiac cycle to the next are far from negligible. Subsequently mean values of the ventricular gradient were obtained from three such cycles. The differences between these means and the time integral of a PVC of the same tracing are shown for 10 randomly selected records in Table III

Using Formula 3 of the appendix, the variance for normal sinus rhythm of these 10 cases was found to be

$$S_{\bar{x}}^2 (X) = 12\ 30$$

$$S_{\bar{x}}^2 (Y) = 47\ 14$$

$$S_{\bar{x}}^2 (Z) = 14\ 71$$

Table III Means of the time integrals of three NSB are shown together with time integrals of PVC of the same record in orthogonal leads X Y and Z

Subject		ÂQRST X	ÂQRST Y	ÂQRST Z	SVG
1	NSB	12 4	−7 8	4 8	15 4
	PVC	19 9	−5 8	19 0	28 1
	D	−7 5	−2 0	−14 2	−12 7
2	NSB	55 0	−21 5	43 3	73 3
	PVC	29 3	−39 3	1 1	49 0
	D	25 7	17 8	42 2	24 3
3	NSB	26 6	10 9	12 0	31 1
	PVC	20 9	11 5	−13 8	27 6
	D	5 7	−0 6	1 8	3 5
4	NSB	17 3	−8 8	2 3	19 6
	PVC	13 3	−28 4	18 1	36 2
	D	4 0	19 6	−15 8	−16 6
5	NSB	−14 5	−23 6	−7 9	28 8
	PVC	−4 7	−5 6	−42 3	42 9
	D	−9 8	−18 0	34 4	−14 1
6	NSB	−5 1	−16 2	9 2	19 4
	PVC	−9 1	−32 3	21 6	40 0
	D	4 0	16 1	−12 4	−20 6
7	NSB	−9 5	−9 6	6 1	14 9
	PVC	24 2	3 3	11 0	26 8
	D	−33 8	−12 9	−4 9	−11 9
8	NSB	24 8	−2 8	−18 8	31 2
	PVC	−20 0	−70 6	−76 3	105 8
	D	44 8	67 8	57 5	−74 6
9	NSB	−3 7	10 2	17 1	20 3
	PVC	11 2	18 9	26 8	34 7
	D	−14 9	−8 7	−9 7	−14 4
10	NSB	79 6	67 7	−39 7	111 8
	PVC	89 0	49 6	−19 7	103 7
	D	−9 4	18 1	−20 0	8 1

D indicates the difference between these values. Ten randomly selected examples are shown. Results are expressed as μV sec. Note the extremely large differences in record 8. Such large discrepancies were found in several other cases.

with M being 9. Formula 5 of the appendix was then used for the determination of the variance of 56 records obtained with the Frank lead system with both NSB and PVC.

$$S_E^2\,(X) = 236.9$$

$$S_E^2\,(Y) = 382.7$$

$$S_E^2\,(Z) = 403.1$$

The same procedure applied to the 15 records obtained with the SVEC III lead system resulted in the following variances:

$$S_E^2\,(X) = 169.3$$

$$S_E\,(Y) = 318.1$$

$$S_E^2\,(Z) = 554.0$$

When the results of the two lead systems were combined for all 71 records, the variances were:

$$S_E^2\,(X) = 222.6$$

$$S_E^2\,(Y) = 369.0$$

$$S_E\,(Z) = 435.0$$

The magnitude of error introduced by the thickness of the tracings in photographic records is shown in Table IV. The spatial angle between SÂQRS obtained by planimetry of QRS areas traced along the upper and lower margins of the records, respectively, showed relatively large discrepancies between these two methods. It may extend to 90 degrees. The error of this graphic method could be somewhat decreased when the center of the trace was used for planimetry, but this procedure is relatively difficult because the thickness of the trace changes with the rate of change in amplitude.

Discussion

The concept of the ventricular gradient encompasses several different aspects of the ECG time integral. The most important and least controversial deals with the difference in time courses between depolarization and repolarization. Already in 1931 Wilson[30] offered several alternate explanations for this phenomenon. Although many others have been added since then, the knowledge of the electrophysiologic basis of the VG has not been advanced significantly. The main difficulty rests upon detailed experimental analysis of repolarization as pointed out again

Table IV. Spatial angles between SÂQRS vectors obtained by different methods of planimetry from identical records

	SÂQRS obtained from upper and lower margins of records	SÂQRS obtained from upper margins and center of tracings	SÂQRS obtained from lower margins and center of tracings
Normal records			
1	9	2	8
2	10	8	4
3	35	20	16
4	42	29	14
5	45	29	25
6	29	21	9
Abnormal records			
7	40	21	20
8	13	14	2
9	90	45	47
10	44	37	8

As expected, differences are largest when time integrals obtained from the upper and lower margins of records were compared. These discrepancies can be reduced somewhat when the center of the trace is followed with the planimeter.

recently by van Dam and Durrer.[21] The fact that differences in time courses between QRS and T exist has never been questioned, however, and is generally accepted.

The second postulate made by Wilson, the constancy of the ventricular gradient in spite of changes in the pathway of ventricular activation, has been challenged repeatedly. Many of the arguments about the validity of this concept are based on questions about methodology. As was shown previously,[4,5] the accuracy of the procedures used for obtaining the time integrals is of crucial importance. Therefore, great care was taken in the present study to achieve the highest degree of accuracy possible by modern equipment and careful statistical evaluation of data. Most previous studies dealing with quantitative aspects of time integrals can be questioned on the basis of inadequate methodology. Simonson and associates[8] were the first to point out that areas measured in Wilson's original papers[1,20] did not support his hypothesis. The ventricular gradient had changed with changes in the conduction pathway. Angle[9] confirmed this observation and also pointed out that in the case of intermittent right bundle branch block, reported by Simonson and associates,[8] VĜ changed significantly with the appearance of the ventricular conduction defect. The large discrepancies between time integrals determined with different methods from photographic oscilloscope records in the present study confirm Angle's observations.[9] Enlargement of records for determination of area improves the accuracy to a limited extent only because the width of the tracings is enlarged at the same time. Electronic integrators or computation of digital records can circumvent this difficulty.

Another large source of error which has not been considered sufficiently is the beat-to-beat variability of time integrals. Since respiratory changes appear to cause most of this variability, VĜ needs to be averaged during inspiration and expiration. As shown in lead Z of Table II, the time integral may increase almost twofold during normal respiration. Such drastic changes occur mainly when the time integral is small or close to zero. The direction of VĜ will also change markedly in all such cases.

The importance of spatial VĜ display is recognized more widely. Burch and associates[22] were the first to report on SVĜ obtained by a VCG lead system, the tetrahedron. Berkun and associates[23] used the cube lead system and examined differences between NSB, PVC, and records with intermittent bundle branch block and the Wolff-Parkinson-White syndrome. In the latter investigation the most drastic changes were found for PVC, but the changes of SVĜ in the remainder of the cases, although far from negligible, were not considered to be significant.

The main difficulty in evaluating these results derives from the known variability in lead strength and direction of the leads of the cube system. This has been shown not only in torso models[18] but also in man.[19] The strength of lead Z averages only 22.5 per cent of that of lead X.[19] This discrepancy in lead strength is too large for quantitative studies because the relatively weak sagittal lead tends to underestimate electromotive forces along this axis.

In more recent years, several applications of corrected orthogonal lead systems for determination of SVĜ have been reported.[24-26] Although very closely related to each other, these systems are not completely identical, and a constant factor needs to be applied for amplitude data in order to make results comparable.[13] In order to minimize the error which might have been introduced by the application of one particular corrected system, both Schmitt's SVEC III[16] and Frank's system[17] were used for testing the significance of differences in SVĜ between NSB and PVC. For both systems, comparable differences of SVĜ were found when the pathway of ventricular activation changed.

From the present study it can be concluded, therefore, that the ventricular gradient obtained from body surface leads does not remain constant when the pathway of ventricular activation changes. These findings are in agreement with the reports by Simonson and associates[8] and Angle,[9] who were unable to confirm Wilson's original hypothesis. The findings from body surface leads may be pertinent

to results obtained from isolated muscle strips or muscle fibers.[17] The reverse is also true because of the known difficulties in translating findings from isolated preparations to the body surface ECG.

There appears to be no doubt about the validity of the main part of Wilson's hypothesis on the difference in time courses between depolarization and repolarization. However, from the present study it appears that studies to elucidate this phenomenon will have to follow rather stringent rules of methodology. Planimetry of graphic recordings, even if enlarged, can easily lead to rather large errors. The same is true when only one cardiac cycle is used for study because of the beat-to-beat variability of $\hat{VG}$. Wherever possible, electronic integrators or digital computers should be used together with averaging techniques of sequences of cardiac cycles.

For clinical applications these pitfalls need to be considered as well. The invalidity of the hypothesis on the constancy of $\hat{VG}$ in spite of differences in the pathway of ventricular activation does not affect the clinical usefulness of this measurement. It has to be remembered, however, that such applications have only a limited value. For the screening of normal and abnormal records, $S\hat{VG}$ proved to be rather effective.[21] A quantitative evaluation of a variety of ECG measurements for their diagnostic discrimination power showed, however, a rather poor performance of $S\hat{VG}$ when a variety of diagnostic entities were considered.[19,21] Spatial maximal vectors, which are much easier to obtain, separated these entities almost as well. Diagnostic discrimination by $\hat{VG}$ seems to be more efficient when specific pathologic entities rather than a large number of possible diagnoses are considered.[19,22] Since $\hat{VG}$ summarizes the electrical events of one cardiac cycle in one single term, it becomes obvious that much detail of the diagnostic ECG information is lost in this process.

Summary

The spatial ventricular gradient was obtained from 71 ECG records exhibiting both normal sinus beats (NSB) and premature ventricular contractions (PVC). The difference in gradients between normal and extra beats was compared statistically with beat-to-beat variability of normal sinus rhythm. A significant difference was found and Wilson's hypothesis on the constancy of the ventricular gradient in spite of changes in the ventricular activation pathway could be rejected. Two different corrected orthogonal lead systems were used in order to minimize the effect that a particular lead design might have had upon results.

Methods for obtaining ECG time integrals were studied for accuracy and consistency. In planimetric determinations the width of records was found to influence results considerably. Digital or analog computations were found to be a preferable procedure for quantitative applications. Furthermore, the averaging of time integrals over at least one respiratory cycle was found to be necessary in order to eliminate beat-to-beat variability of the ventricular gradient. Since methods for obtaining ECG time integrals were found to be very critical, the question was raised whether simpler ECG measurements, such as maximal QRS vectors, are not preferable for clinical use.

Appendix: Statistical estimation and comparison procedures

In this paper, two groups of subjects are being compared. Group "N" (normal) consists of individuals whose VCGs exhibit normal sinus rhythm. Group "E" (extra) consists of individuals whose VCGs exhibit an extra heartbeat. More specifically, the ventricular gradients of the VCGs corresponding to group N are to be compared with those corresponding to group E. The method chosen for comparison is likelihood ratio test for the equality of two variances. The assumptions necessary for its use may be found on page 268 of Mood's book.[23] The procedure used here differs from those only in the method of estimation used. The test is applied to the X, Y, and Z leads separately. The technique will be described for the X lead only. The technique generalizes to the Y and Z leads with obvious changes in notation.

Estimation of variation in group N. For each individual in group N, the ventricular gradient was measured in three complexes

Table V

Lead	S_N^2	Comparison 1		Comparison 2		Comparison 3	
		S_E^2	F	S_E^2	F	S_E^2	F
X	12.50	236.9	18.95	236.9	13.34	222.6	17.81
Y	47.14	382.7	8.12	382.7	6.75	369.0	7.83
Z	14.71	403.1	27.40	403.1	17.81	435.0	29.57

Each F statistic is larger than the $F_{.01}$ value.

of the X lead. Call these X_{i1} and X_{i2} and X_{i3} respectively. The subscript i indicates that these measurements are taken from the i th individual in the group. The average value for the VG in the i th subject is estimated by

(1) $$\bar{X}_i = \frac{1}{3}(X_{i1} + X_{i2} + X_{i3})$$

The variance of the VG for the i th subject is estimated by

(2) $$S_{Ni}^2(X) = \frac{1}{2}\left[(X_{i1} - \bar{X}_i)^2 + (X_{i2} - \bar{X}_i)^2 + (X_{i3} - \bar{X}_i)^2\right]$$

The average variance for the M individuals in group N is estimated by

(3) $$S_N^2(X) = \frac{1}{M}\sum_{i=1}^{M} S_{Ni}^2$$

Estimation of variation in group E. For each individual in group E, the VG's in the X lead of a normal beat and an extra beat were measured. For the i th individual in group E, these will be denoted as X_{Ni} and X_{Ei} respectively. The variance corresponding to the i th individual is estimated by

(4) $$S_{Ei}^2(X) = \frac{1}{2}\left[X_{Ni} - X_{Ei}\right]^2$$

The average variance for the K individuals in group E is estimated by

(5) $$S_E^2(X) = \frac{1}{K}\sum_{i=1}^{K} S_{Ei}^2$$

Comparison of variances. The variances of the two groups are compared using an F statistic

(6) $$F(X) = S_E^2(X)/S_N^2(X)$$

with K and 2M degrees of freedom. Loosely speaking, if this ratio is "large," it would not seem to be reasonable that the variation in the two groups is the same. Large is chosen to mean larger than a number denoted $F_{.01}$ which corresponds to the .01 significance level of the F distribution.

SUMMARY OF RESULTS. In each of the three following comparisons, group N consists of the same 10 cases. This yields a parameter 2M = 18. *Comparison 1.* Group E consists of 56 records obtained with the Frank lead system. This yields K = 56 and $F_{.01}$ = 2.78. *Comparison 2.* Group E consists of 15 records obtained with the SVEC III lead system. This yields K = 15 and $F_{.01}$ = 3.26. *Comparison 3.* Group E consists of the combined 71 records of comparisons 1 and 2. This yields K = 71 and $F_{.01}$ = 2.76. (See Table V.)

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Measurement of pacemaker performance

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This report concerns a simple method of assessing pacemaker function by externally analyzing its signal. The method has proved to be of practical value not only in monitoring pacemaker performance after implantation but also in identifying the cause of failure when and if it occurs. Satisfactory treatment of complete heart block with electronic pacemakers has been complicated by an inability to measure pacemaker function after implantation. The duration of artificial pacing is limited by the life of the individual unit, and when it fails, reimplantation of a new pacemaker is usually mandatory. Routine replacement of each pacemaker after 15 months of service has been recommended as one method of assuring a high probability of trouble-free performance. Such prophylactic replacement is reasonable in the absence of adequate knowledge of pacemaker function after implantation since the only alternative is for the physician to await failure before recommending replacement, thus incurring the risk of untreated complete heart block during the interim period.

Two major problems can be identified in the long-term management of pacemaker patients: first, uncertainty of when a pacemaker will fail, and second, accurate information about the cause for pacemaker failure if it occurs unexpectedly. The former is not only medically important for the protection of the individual patient but economically important for assurance of full use of the pacemaker prior to replacement. The latter is also vital since the management of different types of pacemaker failures varies depending on the cause.[1-4] The method to be described enables the physician to answer both of these vital questions. Although this method is applicable to only one of the commercially available units† at the present time, the problems of management are common to all artificial pacemakers.

Materials and methods

This study consisted of three phases of investigation. During the first phase, in order to analyze the exact shape and magnitude of the pacemaker waveform

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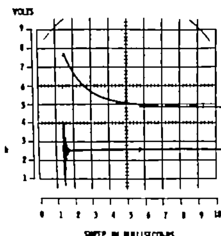


Fig. 1a, Oscilloscopic picture of pacemaker pulse waveform, showing sudden onset, RC decay and abrupt termination. From onset to termination is the pulse width. b, Detector-coil stimulus deflections, coinciding with beginning and end of pacemaker pulse. Note that the onset deflection is greater than the termination deflection, due to greater change in current.

measurements of voltage between the myocardial electrodes were made from a series of 4 dogs with external pacemakers. This was done by using a calibrated cathode ray oscilloscope (Tektronic type 502) capable of pulse synchronization and having a sweep of 1 millisecond per centimeter. Fig. 1,a shows a photograph of the voltage of a pacemaker pulse as seen on the oscilloscope. Multiple measurements were made on each animal and were recorded by means of a Polaroid camera. To measure current a 1-ohm resistance was inserted in series with the heart impedance, and by the same method the voltage across this resistance was measured. The voltage value thus obtained is equivalent to current. Total pulse energy was then calculated from these two curves by multiplying average voltage times average current for each millisecond throughout the pulse and integrating the millisecond decrements of energy for the duration of the pulse.

The second phase of the investigation was the construction of a laboratory model with a simulated interelectrode impedance identical to the biologic impedance as calculated from the dog studies. This model allowed precise variation of load impedance and battery voltage so as to simulate all possible clinical conditions, with measurement of pacemaker voltage and current using the method described above. It was found that, for any biologic impedance an equivalent electrical resistance and capacitance could be substituted.

Investigation showed that the pulse duration or pulse width can be exactly measured by placing a detector coil (7,000 turns of No. 38 magnet wire) on the surface of the skin over the pacemaker unit. Fig. 1,b shows oscilloscopic measurement of the pulse width. It is the distance between the two deflections, due to voltages induced in the detector coil by the rapidly changing currents during the upstroke and downstroke of the pacemaker pulse. The upstroke of the pulse represents a greater rate of change in current than does the downstroke, and therefore induces in the detector coil a greater voltage. The two deflections correspond exactly to the onset and termination of the pacemaker pulse.

The third phase of the investigation was the application of these methods to the human heart. The first step was to make direct measurements of voltage and current from the external pacemaker electrodes of one patient, in order to be sure that there were no significant differences between canine and human cardiac impedances. Then two pacemakers were carefully precalibrated (rate and pulse width determined for a range of biologic impedances) after which they were implanted into patients. Serial measurements were made of exact pacemaker rate and pulse width using the detector method. This was done externally by placing the detector coil over the implanted pacemaker. Finally we applied these methods to a clinical series of 42 patients whose pacemakers were not specially calibrated for all possible impedances.

Results

The studies in dogs showed that an average interelectrode impedance was about 300 ohms resistance and 47 microfarads capacitance. Interelectrode impedance measured from the human heart was not significantly different. Total output of pacemaker pulse energy in dogs averaged 60

microjoules. In the one patient in whom it was measured the pulse energy was 67 microjoules.

The pacemaker used in this study has a resistance-capacitance (RC) discharge waveform as shown in Fig. 1,a. Any biologic load can be replaced by an indistinguishable simulated load of resistance (R_L) in series with capacitance (C_L) as shown in Fig. 2. Using variable simulated interelectrode impedances (R_L and C_L) and varying battery voltage, we found that changes in any of these three parameters were reflected by measurable changes in one or both of two clinically obtainable variables, pacemaker rate and pulse width. Especially noteworthy was the finding that a change in R_L caused a measurable change in pulse width as shown in Fig. 4. Varying R_L did not change pulse rate until R_L exceeded 5,000 ohms. In all animal and human measurements, R_L was in the range of 200 to 500 ohms provided that the pacemaker was functioning normally. We never observed it to exceed 500 ohms. Therefore, it could be concluded that biologic increases in R_L do not affect the pacemaker rate.

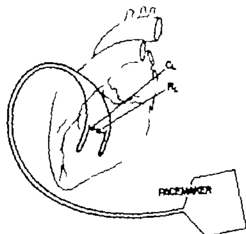


Fig. 2. Schematic representation of pacemaker interelectrode, or myocardial impedance. R_L (load resistance) and C_L (load capacitance) are in series with the pacemaker electrodes.

Changes in C_L, on the other hand, caused a proportionate change in pulse width and an inverse change in pacemaker rate. Fortunately, changes in pulse width were minimal and within the limit of error of the method (1/10 millisecond). Changes in rate, however, were very significant when C_L varied within the observed biologic range. A variation of 20 microfarads produced a detectable variation in rate of 3 pulses per minute in the range of the average biologic value of C_L (47 microfarads). See Fig. 3.

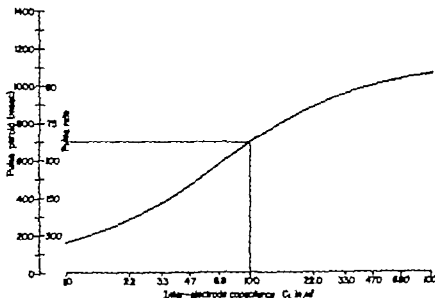


Fig. 3. C_L versus pulse period in milliseconds. The pulse period is the time between pulses. Approximate rates are shown in parentheses. In the example shown, a rate of 86 gives a C_L of 10 microfarads.

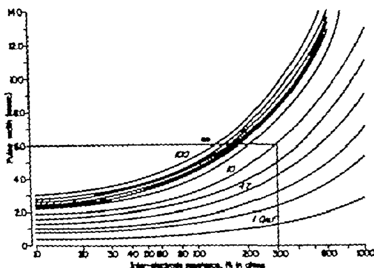


Fig. 4. R_L versus pulse width. In the example shown, for C_L = 10, a pulse width of 6.0 gives R_L = 300 ohms.

Changes in battery voltage also affected both rate and pulse width but to an equal degree. A decrease of [illegible] per cent (0.5 volt) in the voltage of the main battery resulted in a 3.5 per cent increase in rate (2 pulses per minute) and at the same time caused a 4 per cent increase in pulse width (0.3 millisecond). These changes pertain only if the bias battery remains constant. A decrease in the voltage of the bias battery results in a decrease in rate and no change in pulse width.

Application of these observations to the practical problem of monitoring pacemaker function resulted in the following deductions: (1) An isolated increase in pulse width with no change in rate denotes a predictable increase in interelectrode resistance. (2) An isolated decrease in rate with no change in pulse width denotes a predictable increase in interelectrode capacitance. (3) Progressive simultaneous increases in both pulse width and rate most likely represent a decreasing voltage of the main battery. Although this combination could be simulated by an *increase* in R_L with a concomitant *decrease* in C_L, subsequent clinical observations proved that this possibility was unlikely. (4) Abrupt, sizable increases in rate and pulse width with or without variations from one pulse to the next cannot be accounted for by biologic variations in R_L and C_L and therefore can only be produced by a lead fracture, which would suddenly introduce a marked change in both R_L and C_L. Subsequent experience showed that the open circuit produced by an electrode break is frequently bridged by an impedance which may be variable, causing changes in R_L and C_L from one pulse to the next.

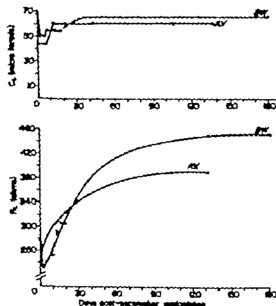


Fig. 5. R_L and C_L versus time for 2 patients with precalibrated pacemakers. Note the rise in R_L while C_L becomes constant after the postoperative period.

Application of these principles to the human problem began by our making serial measurements of rate and pulse width on 2 patients whose implanted pacemakers had been precalibrated by determining rate and pulse width for various values of R_L and C_L within biologic limits. The values of these two variables were determined over a period of 6 months, and are shown in Fig 5 Note that capacitance varies insignificantly after implantation whereas resistance tends to plateau after an initial rise

Measurements were also made on a total of 42 patients whose pacemakers were not precalibrated In 19 of these, serial measurements were made from the day of implantation in 10 serial measurements were made beginning 1 month or more after implantation and in 13 only one measurement was made. See Table I

Discussion

There is general concern that the electrochemical effect of implanted cardiac pacemakers on the tissue surrounding the electrodes, and on the myocardium etween them may ultimately alter pacemaker performance After direct implantation of electrodes the interelectrode impedance with its resultant effect on myocardial threshold has been shown to be ltered by at least three factors (1) the ype of electrodes, (2) the pulse waveform nd (3) foreign body reaction around the lectrodes[1,1] The results of this study how that interelectrode impedance does ary with time in a predictable manner

Other investigators have made analyses of electrical signals coming from implanted pacemakers but these methods have not given definite information of diagnostic value about interelectrode impedance or changes in pacemaker performance[11,12] The key to this method of analysis lies in the circuit design of this particular pacemaker which has an output pulse that is dependent on the load The entire electrical analysis can be performed externally in less than 1 minute without directly touching the skin of the patient and absolutely without harm. For this reason it should have practical clinical value

In determining interelectrode impedance by this method we assume that battery voltage remains constant throughout the period of observation We think that this is valid for three reasons. (1) The pacemaker power supply has been shown to reach a constant mercury voltage level after which there is insignificant variation until the battery energy is near depletion. For the pacemakers used in this series, quality control requires constant output voltage for at least 3 months prior to implantation (2) Serial measurements on five pacemakers incubated at 37°C over a period of 3 years demonstrated no significant changes until one of the component batteries had reached the end of its life (3) The rates of implanted pacemakers have been observed to be unexpectedly constant after the immediate recovery period This means that voltage must also be constant, since the two are interdependent.

For a calibrated pacemaker impedance is determined as follows First the rate is measured accurately and from this rate the interelectrode capacitance is obtained from a plotted graph of C_L versus rate (see Fig 3) Once C_L is known R_L can then be determined from a graph of R_L versus pulse width for various values of C_L (see Fig 4) The results show that pacemaker rate becomes constant within the first 6 weeks therefore interelectrode capacitance must become constant. The serial measurements after implantation in 19 patients with uncalibrated pacemakers, showed a uniformly rising pulse width with constant rate This indicates that the interelectrode resistance in all of these patients (in addition to the 2 patients with calibrated pacemakers) increased during the first 3 months after implantation However serial measurements in 10 cases, beginning at least 3 months after implantation showed no further increases in pulse width This leads to the conclusion that after 3 months R_L remains constant, or nearly so The near-linear increase in R_L during the first 3 months after implantation can be attributed to changes at the electrode surfaces (electrolysis) in addition to fibrosis in the area surrounding the electrodes.

Changes in pacemaker performance result in definite and distinct changes in the

Table I Measurements of pulse width in 19 patients with pacemakers not calibrated for R_L and C_L*

	Pulse width vs days after implantation for 19 patients																		
	H.M	H.H	R.B	M.R	M.Y	B.D	B.H	F.H	L.H	A.V	G.H	F.L.	O.B	B.V	E.L.	П.D	H.П	M.G	Y.S.
0	5.8	6.7	5.8	5.7	—	7.0	8.1	8.2	9.0	6.8	5.6	—	6.1	6.5	6.2	—	8.9	6.0	—
1	0	6.2	—	6.1	—	—	—	—	—	—	—	6.3	—	6.1	6.6	5.3	8.5	—	6.1
2	—	—	5.6	6.1	6.1	6.7	7.3	7.7	8.7	—	5.8	—	6.5	6.0	6.9	—	—	6.0	—
3	6.5	6.5	—	—	6.2	—	7.2	—	—	7.2	—	6.2	—	—	6.9	5.4	8.8	—	5.9
4	6.8	—	5.5	6.3	—	6.8	—	—	8.5	7.3	5.9	—	—	—	7.1	—	—	6.0	—
5	6.9	6.6	—	—	6.2	—	7.3	—	—	—	—	6.4	6.4	—	7.7	5.6	8.9	—	6.1
6	—	—	5.6	—	—	—	7.4	8.4	8.5	7.5	6.0	—	—	6.0	—	—	—	6.0	—
7	—	7.0	—	6.4	—	7.0	7.5	—	—	7.6		6.4	6.6	—	—	5.6	—	—	6.2
8	7.4	7.0	—	—	6.4	—	7.6	—	8.7	—		—	—	5.9	—	—	9.0	—	—
9	—	7.1	—	—	—	—	—	—	—	—		6.6	—	5.9	7.4	5.7	—	—	6.4
10	7.6	—	—	6.5	6.6	7.2	—	—	8.9	—		—	—	—	—	—	—	—	—
11	—	—	—	—	—	—	7.9	—	—	—		—	—	—	—	5.7	—	—	6.4
12	—	—	—	—	—	—	—	—	9.1	—		—	—	—	—	—	—	—	—
13	—	—	—	6.6	—	—	8.1	—		—		—	—	—	—	—	—	—	—
14	7.9	—	—		—	—	—	—		—		—	—	—	—	—	—	—	—
15	—	7.7	—		—	—	—	—		8.0		—	—	—	—	—	—	—	6.4
16	8.1	—	—		—	—	—	—		—		—	—	—	—	—	—	—	—
17		7.8	—		—	—	—	—		—		—	—	—	—	—	—	—	—
18		8.0	—		—	—	8.7	—		—		—	—	—	—	—	—	—	—
19-21		8.3	—		—	—	—	—		—		—	—	—	—	—	—	—	—
22-30		8.3	6.5		—	—	—	—		8.2		7.3	—	7.0	—	—	—	—	6.8
31-40		9.1			—	—	—	—		—		—	—	7.4	—	—	—	—	
41-50					—	—	—	—		9.1		—	—	—	—	—	10.6	6.9	
51-60					—	—	—	—		—		—	7.7	—	—	—		—	
61-70					—	—	—	—		—		—	—	—	9.1	—		—	
71-80					—	—	—	—		—		—	—	—	—	7.7			
81-90					—	—	—	—		—		—	—	—	—	7.6		7.0	
91-100					—	—	—	—		—		8.2	—	8.3	—				
101-110					8.1	—	—	—		9.8		—	7.7		9.6				
111-120					—	—	—	—		—		8.2							
121-130					—	—	—	—		—									
131-140					—	—	—	11.4		9.8									
141-150					—	—	—												
151-180					—	—	10.8												
181-210					—	10.0	—												
211-240					8.1														

I all cases, rate either remained constant or decreased slightly; increasing pulse width is due therefore t increasing interelectrode resistance (See results)

two pacemaker variables, pulse width and rate. The immediate value of these findings is in the differential diagnosis of pacemaker failures and in identifying incipient failures. Fortunately with the pacemaker used there have been no component failures. Therefore, our clinical experience has been concerned solely with differentiating between battery failure electrode fracture, and critical elevation of myocardial threshold

Battery failure was correctly diagnosed by this method in all of 8 cases. Of particular importance is the fact that failure in 5 cases was detected while the myocardium was still responding to the stimulus. The other 3 cases presented after the stimulus level had fallen below threshold and the heart was no longer responding to the pacemaker In 4 of these cases the main batteries were involved and a progressive increase in both pacemaker rate and pulse width was manifest (See Table II.) The other 4 cases involved failure of the bias battery which resulted in decreasing rate without a change in pulse width Each pacemaker has one bias battery which controls switching and deterioration of this battery has the abovementioned effect, which is easy to identify

Electrode breaks were correctly diagnosed in all of a total of 5 cases, and in an additional unit the diagnosis of short circuit of the electrodes was made A short circuit is manifested by a very short pulse width and a constant rate. The 5 instances of wire breakage resulted in sudden increases in pacemaker rate and measurements showed very long and variable pulse widths, in addition to variation in rate from one pulse to the next These changes are caused by an open circuit, giving a greatly increased and variable interelectrode resistance (greater than 5 000 ohms)

Table II. Differential diagnosis of pacemaker failures based on changes in pacemaker rate and pulse width

	Pulse width	Pacemaker rate
Wire break	Sudden increase	Sudden increase
Exit block	Rapid increase	No change
Main battery	Slow increase	Slow increase
Bias battery	No change	Slow decrease

Increased myocardial threshold to a level above the constant-energy pacemaker stimulus, was diagnosed in 11 cases. In 7 of the cases the diagnosis was confirmed by testing the removed pacemaker unit and finding it to be functioning within normal limits, and in 4 cases it has not been necessary to replace the pacemaker We have applied the term exit block to this situation The definition given for exit block is inability of an impulse to leave its point of origin the mechanism for which is conceived as an encircling zone of refractory tissue denying passage to the emerging impulse [13] We think that this term characterizes the clinical situation in which the myocardium becomes unresponsive to a normally functioning pacemaker In our experience, the diagnosis can be anticipated by finding a rising pulse width with a constant pacemaker rate This indicates a rapidly rising interelectrode resistance There was no correlation of exit block with high absolute values of interelectrode resistance but there was a definite correlation with rapidly increasing R_L for any given patient.

We think that, by serial measurements after implantation pacemaker performance can be adequately evaluated so as to make prophylactic replacement of the unit unnecessary Although electrode breaks can not be identified until after a complete fracture occurs, and may always be an unpredictable factor there is hope that improvements in the design of electrodes will drastically reduce the incidence of this type of failure Each of our patients is now asked to record daily his pacemaker rate using a transistor radio held over the unit and he is instructed to report immediately any change in rate greater than 3 pulses per minute Each patient is also asked to attend a pacemaker clinic which is held every 3 months,

for the purpose of taking serial measurements. The method of analysis described requires only the instruments mentioned the type pacemaker used in this study and an adequate knowledge of the pacemaker circuit.[14]

Summary

Entirely satisfactory treatment of complete heart block has been prevented by an inability to measure pacemaker function after implantation. Two major problems can be identified in the long term management of pacemaker patients first adequate prediction of when a pacemaker will fail and second accurate diagnosis of the type of pacemaker failure if it occurs.

Observations on dogs gave precise measurements of interelectrode impedances. A method is described of externally measuring the interelectrode resistance and capacitance of implanted pacemakers. In studies on both dogs and human beings it was found that all changes in interelectrode impedance could be identified by changes in pacemaker rate and pulse width. Serial measurements of these two parameters allowed accurate diagnosis of the different types of "pacemaker failures. The method also enabled anticipation of failures, other than wire breakage, before they were clinically evident. We think that pacemaker performance can be adequately evaluated by this method making unnecessary prophylactic replacement of the unit.

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Occlusive pulmonary vascular disease associated with hemoglobin SC disease

A case report

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In the past decade many of the clinical features of sickle cell disease have been recognized in patients with sickle cell trait and with sickle trait in combination with other abnormal hemoglobins. Thus such complications as salmonellal septicemia aseptic necrosis of the femoral head cerebral vascular accidents, bouts of hemolysis, hyposthenuria and splenic infarction have been reported [1,2] Well-documented instances of the occurrence of pulmonary hypertension and cor pulmonale in patients with sickle cell trait or sickle hemoglobin in association with some other abnormal hemoglobin are unusual however This complication first described in sickle cell disease by Yater and Hansmann[3] in 1936 is presumably due to in situ pulmonary thrombosis of the small peripheral pulmonary arteries Each of these vascular insults adds slightly to the burden of the lesser circulation until after many years cor pulmonale may supervene Clinically some of the isolated episodes may be recognized as "sickle cell pneumonitis," a diagnosis which should be suspected when bacterial confirmation cannot be obtained for what otherwise would appear to be pleurisy or pneumonia At first this diagnosis was made only in patients with sickle cell disease but in recent years there have been a number of reports of pulmonary infarction in those receiving only a single dose of the sickle gene in combination with either single doses of adult hemoglobin or single doses of some other abnormal hemoglobin [4,5] These have resulted in a number of physiologic studies designed to elucidate the pathogenesis and frequency of the problem and in the prognostication that some patients heterozygotic for hemoglobin S would appear with far advanced cor pulmonale due to this cause. The patient whose case is to be described in this report is one of the first with a hemoglobinopathy other than pure sickle cell disease to have developed well-documented fatal cor pulmonale secondary to in situ pulmonary thrombi.

Case report

H McK. a 38-year-old Negro spray painter was first aware of anemia at age 19 when while serving with the United States Army in the South Pacific he was hospitalized for suspected malaria He reported that his sickle cell preparation was positive at that time. Subsequently the patient had num

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erous hospital admissions for a variety of causes. His intake of alcohol grew large over the years, and a number of visits were related to gastric and duodenal ulcers as well as pancreatitis. There was, however, another train of admissions beginning in 1944 at age 21 for complaints referable to the heart and lungs. While still in the Army he was admitted to the United States Naval Hospital, Camp LeJeune, N. C., because of "pleurisy." In 1949 he suffered for 3 weeks with cough and pleuritic pain, which subsided spontaneously. A chest x-ray film taken at that time was reported to reveal linear and patchy densities in both upper lung fields. He was hospitalized in 1957 complaining primarily of dyspnea, swollen ankles, and pain in the left heel. A hematocrit was 38, and, for the first time, a hemoglobin electrophoresis was performed, with the pattern being that of SC disease. He had no further trouble until May, 1962, when he was admitted to Temple University Medical Center because of complaints which he said were identical to those which he had had in 1957. At this time he denied chest pain and had no evidence of orthopnea. He was, however, dyspneic on the slightest exertion. Physical examination revealed a young Negro male who was comfortable at rest, with normal vital signs. The neck veins were distended at 45 degrees, and the hepatojugular reflux was positive. There was moderate generalized cardiomegaly without specific evidence of either right or left ventricular hypertrophy. The second sound at the base was accentuated and demonstrated fixed splitting. There was a Grade 2 to 3 harsh blowing low pitched pansystolic murmur which increased in intensity during inspiration, and which was best heard along the left sternal border (Fig. 1). The liver was enlarged, the lower border extending 5 cm. below the right costal margin. No splenomegaly was noted. The legs were moderately edematous from the ankle to the mid thigh, and moderate clubbing of the fingers and toes was present.

Chest x-ray films revealed generalized cardiomegaly with small bilateral pleural effusions and bilateral hilar congestion (Fig. 2A). The mean QRS axis on the electrocardiogram (Fig. 3) was +75 degrees. There was counterclockwise rotation and evidence of right ventricular hypertrophy with an intrinsicoid deflection of 0.04 second in Lead V_1. Other pertinent laboratory studies included a hemoglobin of 12.9 with a hematocrit of 38 per cent, red blood cell count of 4.85 million, and reticulocyte count of 4.7 per cent. The peripheral blood smear revealed a moderate number of target cells and occasional Howell-Jolly bodies. The presence of SC disease was confirmed by hemoglobin electrophoresis. Extensive studies to elucidate the cause of the patient's difficulties were deferred until after

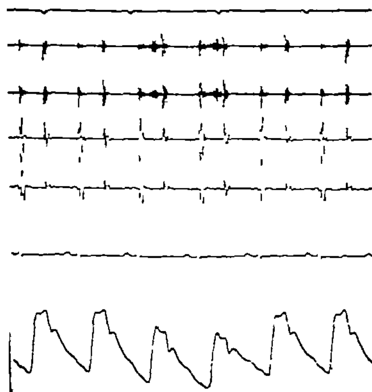


Fig. 1. Phonocardiogram taken along left sternal border in the fourth intercostal space. The upper two recordings are at low frequency and the lower two at high frequency. The murmur increases in intensity and duration during inspiration, as noted by a decrease in the height of the carotid pulse (lowest trace).



Fig 2A Chest X-ray taken on admission to the hospital showing cardiomegaly, pulmonary congestion, and small pleural effusions.



Fig 2B Chest X-ray taken before catheterization and after treatment for congestive failure. It is within normal limits.

he was successfully treated for congestive heart failure Normal or negative studies included the determinations of blood urea nitrogen, blood sugar serum calcium, electrolytes, cholesterol, proteins, and albumin-globulin ratio, x-ray films of the hands and feet axillary node biopsy and skin tests for histoplasmosis, coccidioidomycosis and blastomycosis. The urinalysis was normal, except for a fixed specific gravity at 1.010 and the PPD No. 1 was positive.

On May 14 1962 cardiac catheterization was undertaken At this time the chest x-ray film (Fig 2B) had returned to normal. The results are summarized in Table I An elevated right ventricular systolic pressure, an elevated pulmonary arterial pressure normal wedge pressure low cardiac output and increased pulmonary vascular resistance were found. This combination of findings is indicative of pulmonary hypertension secondary to pulmonary disease. No evidence of shunt could be found from the oxygen curves or angiocardiography The finding of normal lung fields on the chest x-ray films and pulmonary hypertension suggests pulmonary vascular occlusion as the underlying problem This diagnosis was further strengthened by ventilatory studies (Table I) which were entirely within normal limits. In order to establish the diagnosis firmly an open pulmonary biopsy was performed on June 25 1962 Unfortunately the findings were not considered to be indicative of any specific disease and he was discharged without the establishment of an etiological diagnosis. He had, however had one bout of thrombophlebitis during hospitalization, and the possibility was considered that he was suffering the consequences of multiple pulmonary emboli.

The patient remained well until September 1963 when he suddenly developed dyspnea, cyanosis, and tachypnea. On admittance to the emergency room he was found to be acutely and critically ill. Distention of the neck veins, a right parasternal heave, and right ventricular gallop were noted just prior to death shortly after admission. A carbon-dioxide determination performed on the venous blood at this time was 14 mEq per liter Unfortunately the other electrolytes were not determined, so that it is not possible to interpret this finding completely but it is certainly compatible with hyperventilation secondary to alveolar-capillary block

Pertinent findings at autopsy included the following the heart was dilated and weighed 380 grams. The thickness of the left ventricular wall was 1.5 cm that of the right was 8 to 9 mm indicating right ventricular hypertrophy The lungs were congested and edematous. No pulmonary emboli were found. Sections of the lungs (Fig 4,A and B), however revealed multiple occlusions, both old and recent, in the small pulmonary arteries. The spleen was shrunken and fibrotic, and sections revealed evidence of autosplenectomy similar to that seen in the homozygous sickle state

Discussion

The existence and severity of the cor pulmonale in this patient was well established by the clinical history physical examination and physiologic data Yet a diagnosis in this patient was elusive and none of the many consultants who saw him suggested the correct one A biopsy would have been expected to help but apparently an uninvolved section of lung was selected

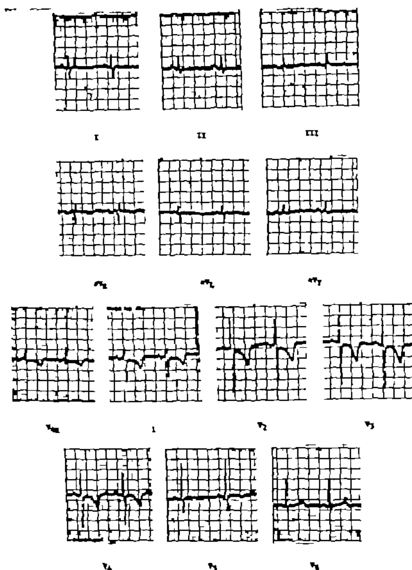


Fig. 3 Electrocardiogram. Right ventricular hypertrophy is clearly evident.

for study. Thus it was not until the post mortem that the precise anatomic correlation previously sought was obtained. This provided clear-cut evidence of chronic occlusive pulmonary arterial disease with cor pulmonale. Whether some of this was on the basis of embolization must, as always, be an open question, especially since he had had at least one episode of thrombophlebitis. The postmortem finding of an autosplenectomy, however, suggests an in situ thrombotic process, since this event, unusual in SC disease,[4] is generally ascribed to this cause. It should be recognized, however, that the arterioles of the spleen and lung are quite different and that this can only be a matter of conjecture.

The natural history of the development of this disorder began in our patient some 19 years prior to his death, when he had had his first episode of pleurisy. That bouts of thrombosis with infarction leading to cor pulmonale might be recognized in patients with hemoglobin S in a variety of combinations (SS, SA, SC, S-thalassemia) was suggested by Moser and Shea in 1957. Seven patients in which the diagnosis

Table I. Findings in Patient H. McK., age 36, B.S.A. 1 7 M²

Cardiac catheterization

	Pressure (mm. Hg)	*Mean pressure (mm. Hg)*	*O content (vol. %)*	*Saturation (%)*
SVC	—	—	11 6	
RA	—	3	11 6	
RV	47/0	—	12 2 11 9	
PA	47/19	27	12 1	
PCP	—	6	—	
LA	a-9 v-7	6	—	
LV	104/8	—	17 9	92

Cardiac output	2 2 L./min.
Cardiac index	1 3 L./min./M²
Total pulmonary vascular resistance index	1 661 dynes/sec./cm.⁻⁵
Pulmonary arteriolar vascular resistance index	1 291 dynes-sec./cm.⁻⁵

Pulmonary function studies

MVR	9 98 L./min.
Inspiratory capacity	1 360 ml.
Expiratory reserve volume	1 450 ml.
Tidal volume	408 ml.

	Actual	*Predicted*	*% of Predicted*
Vital capacity	3 030 ml.	3 965 ml.	77
MBC	92 7 L./min.	116 L./min.	80

Timed vital capacity	*One second*	*Second second*	*Third second*
	85%	95 6	100%

pulmonary infarction seemed to be reasonable were described. In none of these was a source of embolization found. Each had evidence of a hemoglobinopathy involving sickle hemoglobin. Three had homozygous sickle disease, 2 probably had sickle-thalassemia, 1 had sickle trait, and 1 was found to have SC disease. There was insufficient evidence to make the diagnosis of cor pulmonale in any, but it appeared to be likely in at least 2. The authors predicted that as patients with sickle hemoglobin in all its possible genetic combinations lived longer and as medical facilities became increasingly sophisticated, more and more instances of chronic cor pulmonale would be reported on this basis.

Subsequently, Rahimtoola and associates[3] reported 3 cases in which the diagnosis of pulmonary infarction seemed to be reasonable. Two of these patients were found to have sickle trait and 1 to have hemoglobin SC. The authors believed that in situ thrombosis secondary to sicklemia was a likely cause; however, the question of embolization arose in 2. One developed thrombophlebitis shortly after his pulmonary complaints began, and the other was desperately ill with probable empyema prior to the appearance of the pulmonary infarctions. None of the 3 were followed long enough to know whether cor pulmonale occurred.

These clinical reports do not, however, give any indication of the frequency of in situ pulmonary thrombosis or of its complication, cor pulmonale. At least three groups have attempted to ascertain this by performing special studies on groups of patients with sickle hemoglobin. Moser and associates[7] investigated 10 patients with sickle cell disease. They were able to measure the arterial-alveolar gradient for oxygen successfully in 8 of these. Only 2 had normal values at rest, and in 1 of these the values became abnormal after exercise. Only 1 of their patients did not sustain an increase in the gradient after exercise. Cardiac catheterization was carried out in 9. All had normal mean pulmonary arterial

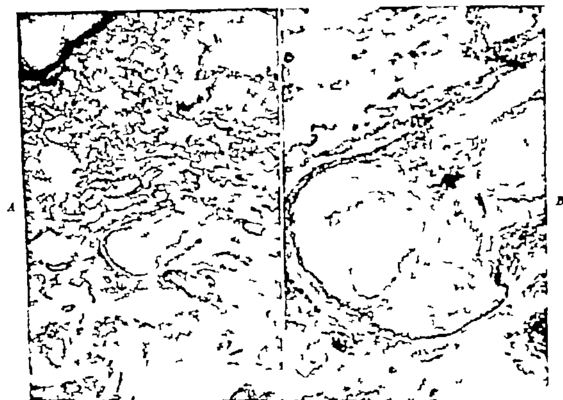


Fig 4 *A* Photomicrograph of lung × 100, reduced 1/6. Elastic tissue stain. Five channels recanalizing an occluded pulmonary artery are easily seen. *B* Same view as in *A* ×430 reduced 1/6

pressures at rest. Exercise produced no change in one third of them an increase to top normal in one third and an increase to abnormally high values in one third These authors presented pathologic data on another patient which clearly showed thrombotic obliteration of small pulmonary arteries and arterioles, and concluded that the cause of the abnormalities noted in their studies was on this basis, with the development of an alveolar-capillary block and secondary pulmonary hypertension Many theoretical factors believed to favor this hypothesis were discussed and the postulation was made that this was a common cause of heart failure in sickle cell disease. The data and hypothesis were in accord with those of Leight and associates, who had previously studied 13 patients with sickle cell disease, one of whom had definite pulmonary hypertension presumably on the basis of in situ thrombosis.

The conclusions of these two workers are however in contrast to that of Sproule and associates, who approached the problem in a somewhat different and more complete fashion in a study of 21 patients with sickle states. Four patients were heterozygous for sickle hemoglobin 4 had SC hemoglobin and 13 were homozygous for sickle hemoglobin. Routine pulmonary ventilation studies and cardiac catheterization were performed and arterial-alveolar oxygen gradients at three different oxygen tensions were determined Sixteen of the 21 patients, 9 of whom had cardiomegaly and dyspnea were found to be desaturated while breathing room air at rest. The mean arterial PO was 63.2 mm Hg with an oxygen saturation of 89 1 per cent and an average gradient of 36 mm Low oxygen breathing decreased and high oxygen breathing increased the gradient, strongly suggesting that the shunting of blood rather than an alveolar capillary block was the cause of the desaturation Furthermore these authors were unable to demonstrate pulmonary hypertension in any of their patients Thus, they concluded that if in situ thrombosis occurs in patients

with sickle cell hemoglobin it must be unusual and that congestive heart failure in such patients is usually due to some other cause

The case presented in this report does not in any way settle the previous difference of opinion It does indicate however that in situ pulmonary thrombosis is a possible cause of heart failure even in patients with only a single dose of the sickle gene Whether the additional presence of hemoglobin C in any way modifies the expression of this capacity of hemoglobin S is, of course unknown at this point. Furthermore this case indicates the need for early diagnosis because if anticoagulant therapy for instance is to offer anything in the way of treatment it must be administered at a reasonably early stage of the disease. It is hoped that the presentation of this case will stimulate the search for an early diagnosis of others so that attempts at therapy may be reasonably evaluated

Summary and conclusions

A case of hemoglobin SC disease is presented in which multiple clinical attacks of pleurisy over the course of many years preceded the development of fatal cor pulmonale The autopsy findings indicated that in situ pulmonary thrombosis was the underlying cause. The pertinent literature on the subject is reviewed and it is concluded that although this complication is more common in pure sickle cell disease it may occur in patients receiving only a single genetic dose of hemoglobin S The role of hemoglobin C in modifying this capacity is unknown The authors believe this case to be the first of a sickle hemoglobinopathy other than pure sickle cell disease in which the patient was extensively studied during life with subsequent anatomic correlation

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Tetralogy of Fallot

Report of case with total correction at 54 years of age

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As the risks of cardiac surgery decrease, new categories of patients can be added to the list of those for whom surgery is indicated. Congenital defects can be corrected before symptoms develop and before irreversible changes occur in the myocardium or pulmonary vasculature. The entire concept of the inoperable lesion or the inoperable situation must be subject to constant review. This is especially true in the case of patients with congenital heart disease who have reached middle age and have, therefore, in many cases, already attained an age in excess of their life expectancy. The surgical risk in the middle aged patient is increased because of age and associated cardiovascular disease, such as atherosclerosis, as well as by the presence of noncardiac disease.

This report documents the case of a 54-year-old man with tetralogy of Fallot in whom the lesions were totally corrected surgically by the use of cardiopulmonary bypass, with good result.

Case report

The patient, a male, was first seen at the Johns Hopkins Hospital in April, 196., at the age of 53. A heart murmur had been present since birth. There was no history of squatting or cyanosis in childhood, and the patient and his wife had been unaware of cyanosis or unusual shape of the fingernails until these features had been called to their attention in late 1961. Although the patient had earlier held jobs requiring moderate to heavy exertion, in recent years he had worked as a supervisor. He had had life-long exertional dyspnea but had never considered it to be limiting or significant; however, the patient minimized his symptoms.

In August, 1961, at the age of 52 years, he had an episode of diplopia and staggering without unconsciousness or paresis. After hospitalization, the symptoms in the central nervous system disappeared, but cyanosis was noted and a phlebotomy was performed. Twelve phlebotomies were performed between August, 1961, and April, 1962. There were no further cerebral vascular symptoms.

On examination (April, 1962) he was a well-developed, mildly obese white man who appeared to be older than his age. The blood pressure was 150-190/80 mm. Hg. The fingers showed minimal clubbing, but there was severe cyanosis, and the patient appeared to be breathless at rest. The jugular veins were distended, and v waves were evident when the patient was lying flat. Palpation of the precordium failed to reveal a thrill or abnormal pulsation. On auscultation, the rhythm was regular and the heart sounds were of good quality. The second sound in the pulmonic area was single and not accentuated. There was a holosystolic murmur with mid-systolic crescendo heard best along the left sternal border in the third and fourth intercostal spaces but widely transmitted to the axilla and back. No diastolic murmur was heard. The lungs were clear. The edge of the liver was felt 3 cm. below the costal margin.

Admission hematocrit was 71 per cent, platelet count 157,000, and uric acid 8 mg. per cent. The

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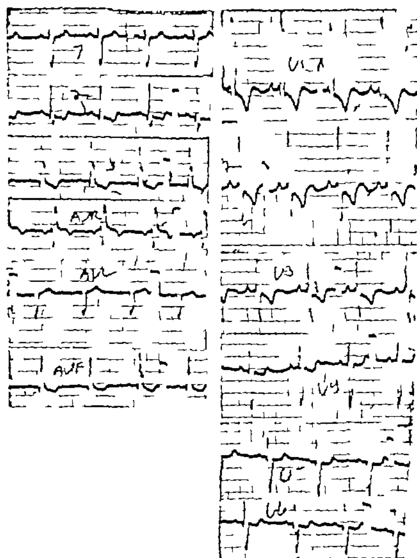


Fig. 1. Electrocardiogram at the time of admission to the hospital. See text.

electrocardiogram showed right axis deviation and right ventricular hypertrophy with an R_{V_1} measuring 28 mm., S_{V_1} 11 mm., R 8 mm., R 3 mm., S_1 12 mm., and a QRS duration of 0.10 second (Fig. 1). Pulmonary function studies showed a normal vital capacity and normal diffusing capacity (using carbon monoxide). There was mild airway obstruction which was lessened by isoproterenol. There was a marked degree of hyperventilation at rest. The chest x-ray films showed right ventricular hypertrophy but no over-all cardiomegaly. Calcium was seen in the aortic arch. The pulmonary vascularity was decreased (Fig. 2).

Cardiac catheterization and cineangiocardiography were performed percutaneously from the right femoral vein. Pressure, flow, and oximetry data are shown in Table I. The findings were typical of tetralogy of Fallot with no valvular pulmonary stenosis, low pulmonary blood flow, and low arterial oxygen saturation. A selective right ventricular cineangiogram showed an extremely trabeculated hypertrophied right ventricle, with severe infundibular stenosis and a large ventricular septal defect. The pulmonary artery appeared to be of adequate size, and there was only mild widening of the aorta.

One day after the catheterization the patient developed typical podagra of the right great toe which responded dramatically to colchicine. The patient returned home after this hospitalization, but he continued to have easy fatigability and dyspnea on exertion which forced him to give up his job. Two weeks after discharge he had a complicating phlebitis of the right leg which responded satisfactorily to conservative therapy.

He returned to the hospital in August, 1963, for operation. The defects were corrected through a longitudinal ventriculotomy during 1 hour of car



Fig. 2. Chest roentgenograms before and after operation. See text.

Table I. Pressure flow and oximetry data

	Pressure (mm. Hg)	*Oxygen saturation (%)*
IVC		63
SVC		61
RA	a = 16, v = 7, m = 6.5	63
RV (body)	125/0/10	62
RV (infundibulum)	18/0/4	61
PA	21/10	61
FA	144/87	79
"PC"		94

Oxygen capacity 29.6 mL per cent
Pulmonary blood flow (Fick) 1.6 L./min./M

diopulmonary bypass. An opening in the infundibular stenosis was found with difficulty and was no more than 2 mm. in diameter. Sixteen grams of muscle were removed. The pulmonary valve and artery were normal. A 2-by 2.5-cm. defect of the membranous septum was closed with a patch of Teflon felt. After completion of the repair identical systolic pressures of 25 mm. Hg were found in the pulmonary artery and right ventricle. The immediate postoperative course was uncomplicated except for pneumonitis in the right upper lobe which responded satisfactorily to antibiotics.

After discharge the patient developed homologous serum jaundice, from which he convalesced without difficulty. He increased his activities, and 6 months after operation he was able to return to his former work, to climb steps, and to perform any physical activity required, without symptoms. He has subsequently worked regularly and requires no medications.

The patient was seen 23 months after operation. There was a Grade 2 systolic murmur along the left sternal border. There were no findings of congestive failure. The hematocrit was 44. The chest roentgenogram suggested a slight decrease in heart size when compared to that taken prior to operation (Fig. 2). The electrocardiogram showed right bundle branch block, which was evident in the immediate postoperative period. During the several months prior to his recent examination, he had developed chest pain which was not typical but which had some of the features of angina pectoris.

Discussion

The survival of patients with acyanotic congenital heart disease into middle and late adult life has been emphasized recently and successful correction of atrial septal defects in patients more than 60 years of age has been reported.[1-4] Such longevity in individuals with cyanotic congenital heart disease is much less frequent and survival past 40 years is quite uncommon.

It is estimated that 1 out of 5 persons with cyanotic congenital heart disease survives to puberty and 1 out of 10 to age 21. Tetralogy of Fallot is the most frequent lesion associated with prolonged survival.

The patient whose case is reported here is one of the older individuals with tetralogy of Fallot who has been reported on in the medical literature and may be the oldest in whom the diagnosis has been established during life and successful total correction carried out. Fallot's original report was of 3 cases, in patients 36, 19, and 26

years old.[5] The longest survival on record was reported by Bain[6]: the patient died of metastatic prostatic carcinoma at the age of 79. A number of patients surviving more than 40 years has been reported[7-11] and a few surviving more than 50 years.[12-17] In one instance, a patient of 53 years was successfully operated upon.[18]

The factors that permit such long survival are not clearly understood but the severity of the pulmonary stenosis and the degree of development of bronchial collaterals must be primary factors, since survival beyond childhood in the presence of pulmonary atresia is an extreme rarity. Hence, in the patient reported on here who had a surprisingly severe infundibular stenosis at operation, the possibility that the infundibular stenosis had become more severe with the passage of time must be considered, since such long survival and relatively symptom-free life seem to be remote in the presence of life-long obstruction of the severity identified at operation. The problems associated with infundibular stenosis as it occurs, progresses, and regresses after operation in cases of valvular pulmonary stenosis and intact septum have been discussed by a number of authors and reviewed by Brock.[19]

Burch and associates[7] has recently suggested that patients with tetralogy of Fallot associated with unusual longevity regularly demonstrate a well-developed left ventricular muscle mass which can be anticipated from the electrocardiographic potentials over the left heart. The electrocardiogram in the case reported here was typical for tetralogy, and, in addition, the auscultatory and roentgenographic findings present in Burch's cases were not found here.

It is worth emphasizing that this patient had no difficulties in the postoperative period to suggest that the pulmonary vascular bed was unable to accommodate a normal flow of blood. His postoperative pulmonary problems seemed to be clearly related to signs and roentgenographic findings of a pneumonitis, and at no time did he have right ventricular failure. Rich[20] first pointed out that severe pulmonary stenosis leads to widespread pulmonary vascular changes, including thromboses and changes in the arterial walls. Fragoyannis and Kardalinos[21] and Heath and associates[22] confirmed Rich's observations and demonstrated that the severity of the pulmonary vascular changes can be correlated with the reduction in pulmonary blood flow and its duration. In Heath's report, all patients over 15 years of age with reduced pulmonary flow had significant vascular changes. In light of these observations, this patient's failure to have any postoperative problems attributable to pulmonary vascular disease is of interest.

This patient suffered several of the more serious complications which occur in individuals with cyanotic congenital heart disease. Cerebral complications such as those seen in this patient are the result of high blood viscosity and anoxia or thrombosis, resulting in an area of softening or infarction. It seems to be likely that the high blood viscosity was a contributor to his postcatheterization phlebitis. After the catheterization the patient developed podagra, which responded dramatically to colchicine and was associated with a high uric acid. The severity and duration of the polycythemia in this patient is such that gout would not be unexpected according to Sommerville.[23] She reported on 9 patients with cyanotic congenital heart disease with gout, all of whom had a hemoglobin greater than 130 per cent and were more than 18 years of age.

The operative result in the patient reported on here, with return to normal activity, is gratifying. This case emphasizes the need to make an anatomic and physiologic diagnosis in patients with cyanotic congenital heart disease irrespective of age. Successful total correction was accomplished in middle life, and it seems to be certain that this patient's life expectancy has been significantly increased by the operation, since improvement in cardiac function and concomitant reduction in polycythemia has been achieved.

Conclusion

A 54-year-old man was studied because of symptoms in the central nervous system and polycythemia. He was found to have a tetralogy of Fallot, which was successfully treated surgically by total correction of the anatomic defects. He is apparently the oldest individual in whom tetralogy

of Fallot has been diagnosed during life and successfully treated

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Mitral insufficiency due to rupture of chordae tendineae simulating aortic stenosis

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Aortic stenosis may be simulated by mitral insufficiency in patients with rupture of the chordae tendineae[1-4] The mitral insufficiency in the following cases resulted from rupture of the chordae tendineae which was not suspected prior to cardiotomy in the first patient, but which was suspected in the second patient Successful repair was achieved in the second patient

Case report

Case I A 54-year-old white man was admitted to the Veterans Administration Hospital, Memphis, Tennessee on Nov 12, 1963 He had considered himself to be well until April, 1963 at which time he noted a nonproductive cough and exertional dyspnea without chest pain He responded to digitalis therapy and returned to work. His symptoms returned in September 1963 and he was again treated for congestive failure Two weeks prior to his admission to the Veterans Administration Hospital he had a recurrence of the exertional dyspnea and noted pedal edema and a dull aching pain in the right upper quadrant. There was no history of rheumatic stigmata bacterial endocarditis, chest trauma hypertension or syphilis. His blood pressure was 130/84 mm Hg the pulse was 56 and irregular due to ventricular premature contractions. A systolic thrill was present at the apex and at the right second intercostal space A Grade 4/6 systolic crescendo-decrescendo "ejection murmur was heard at the right second intercostal space and was transmitted to the neck and to the entire anterior chest, as well as paravertebrally in the left chest After the compensatory pause following a ventricular premature contraction the murmur appeared to be less intense. The murmur did not appear to vary in intensity with the respiratory cycle The second sound was split normally with inspiration. The liver was palpable 5 cm below the right costal margin in the right mid-clavicular line There was pitting edema to the mid-thigh.

The electrocardiogram indicated left ventricular hypertrophy digitalis effect and bigeminy due to ventricular premature contractions. There was absence of septal q in Leads V and V The chest x-ray film (Fig 1) indicated a cardiothoracic ratio of 21/34 cm. with increased pulmonary vascular markings. Planigrams revealed no calcification regional to the aortic or mitral valve On Dec 19 1963 transseptal catheterization indicated increased left atrial pressures and no gradient across the aortic valve (Table I) Mitral insufficiency was confirmed by cineangiography

With the usual cardiac regimen the patient became free of edema and relatively asymptomatic at rest With compensation the intensity of the systolic murmur did not change. The electrocardiogram (Fig 2) continued to show left ventricular hypertrophy and absence of septal q. At operation on Jan 22 1964 slight dilatation of the mitral anulus was noted, and definite interruption of the chordae tendineae of the aortic leaflet of the mitral valve producing marked mitral insufficiency The heart was markedly enlarged with biventricular hypertrophy After insertion of a Starr valve ventricular fibrillation occurred but reverted twice However cardiac action could not be maintained and the patient died.

Necropsy indicated replacement of the myocardium by hyalin at the tip of the posterior papillary muscle with hypertrophy of the papillary muscle fibers. The coronary vessels were patent and no scars were noted in the myocardium

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Fig. 1. Case I. Chest roentgenogram.

Table I. Case I—Catheterization data

Catheter position	Pressures (mm. Hg)	
	Phasic	Mean
Right atrium	11 5/4	7 5
Right ventricle	82/5-12	36
Pulmonary vein	63/6	29
Left atrium	62/8	29
Left ventricle	103/2 16	43
Left ventricle	102/4-14	
Brachial artery	105/69	

*Simultaneous recordings

Comment

This patient presented with signs and symptoms of congestive failure with an ejection murmur thought to be classical of aortic stenosis. Cineangiography was performed prior to aortic valve surgery only to reveal mitral insufficiency without any other significant valvular disease. An attempt to replace the mitral valve which was insufficient because of disruption of the chordae tendineae at the tip of the posterior papillary muscle, resulted in the death of the patient.

Several clinical features in this patient should have suggested that his murmur might be originating from the mitral valve rather than from the aortic valve. A palpable thrill at the aortic area does not always signify aortic stenosis. The fact that the systolic thrill at times is maximal at the apex with aortic stenosis is a well-established fact but the converse—a palpable thrill at the aortic area with mitral insufficiency —is less well appreciated.[5] However, this is not an infrequent situtation with rupture of the chordae tendineae of the posterior leaflet of the mitral valve.[2-4]

The murmur of mitral insufficiency, as in this patient, may be widely transmitted to the back and to the left axilla, whereas with aortic stenosis the murmur is transmitted upward into the neck and at times to the apex. As pointed out by Levine and Likoff,[6] however, any murmur of sufficient intensity, despite its site of origin, may be transmitted widely. In fact, it may be heard quite well in the aortic area, carotid

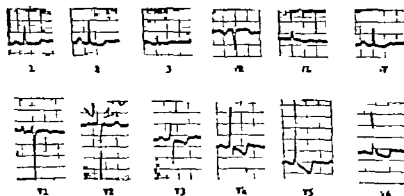


Fig. 2. Case I. Electrocardiogram.

arteries in the back, and sometimes even over the skull

After a compensatory pause the murmur was not intensified which should have been a clue that it was emanating from the incompetent mitral valve although exceptions to this rule have been noted [7,8] The second sound was split normally with inspiration whereas one might have expected a paradoxical splitting of the second sound which is often seen in the presence of aortic stenosis [19]

Hemodynamic studies, including cineangiography indicating predominant mitral insufficiency in the face of the clinical picture of aortic stenosis should have raised a strong suspicion of rupture of the chordae tendineae. Especially is this true in patients who have no history suggesting rheumatic hypertensive or arteriosclerotic heart disease.

Case report

Case II A 53-year-old white man was transferred on Feb. 26 1964 to the Veterans Administration Hospital, Memphis, Tennessee, from the Veterans Administration Hospital, Bay Pines, Florida for possible cardiac surgery. Three years before, the patient had begun to experience slight dyspnea on exertion Cardiac enlargement and mitral stenosis were said to be present He had received digitalis for a period of 4 months, without any appreciable change in symptomatology Digitalis was later resumed in December 1962 and continued thereafter In June 1963 the patient underwent cardiac catheterization elsewhere and major mitral insufficiency and minimal mitral stenosis were allegedly found In January 1964 he experienced increasing dyspnea on exertion and at rest, with intermittent pedal edema. He had not worked at his usual occupation as a bricklayer for a year or two. There was no history of hemoptysis, night sweats, or rheumatic stigmata The blood pressure was 118/70 mm. Hg; the pulse was 68 A harsh ejection murmur was best heard at the right second intercostal space and was transmitted to both sides of the neck. There was a loud whistling pansystolic murmur at the apex and over the entire posterior thorax. A palpable thrill was present over the second right intercostal space and at the apex. The electrocardiogram (Fig 3) indicated left ventricular hypertrophy intraventricular conduction defect, and loss of septal q in Leads V_5 and V_6. The chest x-ray films (Fig 4) indicated cardiac enlargement primarily of the left ventricular type. The phonocardiogram (Fig 5) showed an ejection "diamond-shaped" systolic murmur Cardiac catheterization data (Table II) on March 24 1964 revealed a high diastolic pressure in the left ventricle and an arterial oxygen desaturation indicative of myocardial failure. There was no significant gradient across the aortic valve (10 mm. Hg). By cineangiography moderate mitral insufficiency was noted without other significant hemodynamic lesions, except for the possibility of minimal aortic stenosis. Clinically it was considered that the patient had predominantly mitral insufficiency and that the etiology was unknown but that rupture of

Table II Case II—Catheterization data

Catheter position	*Pressure (mm Hg)*	
	Phasic	*Mean*
Left ventricle	110/9-14	48
Femoral artery	117/69	84
Aorta	114/80	91

Pull back pressure from left ventricle, 124/6-21 to aorta, 114/80
Arterial oxygen saturation 93 per cent

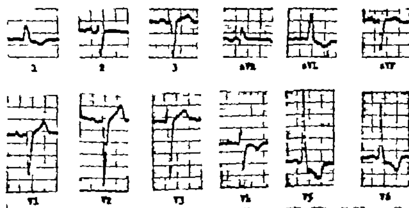


Fig 3 Case II Electrocardiogram.



Fig. 4. Case II. Chest roentgenograms.

the chordae tendineae to the posterior leaflet of the mitral valve could not be excluded. On April 3, 1964, at operation under cardiopulmonary bypass, the left ventricle and left atrium were found to be greatly enlarged. A thrill was palpable over the left atrium. The annulus of the mitral valve was considerably dilated with rupture of the chordae tendineae from the tip of papillary muscle to the posterior leaflet, which was able to flap freely. The leaflets were reefed up, using interrupted sutures of Tevdec, and the annulus was reduced in size with additional interrupted sutures of O Tevdec. The remnants of the chordae tendineae were excised. The valve then appeared to be competent. After the operation the auscultatory findings remained essentially unchanged except for a decrease in the intensity of the murmur and the absence of a palpable thrill (see phonocardiogram, Fig. 5). Atrial fibrillation occurred after the operation but reverted to sinus rhythm with quinidine therapy. The electrocardio-

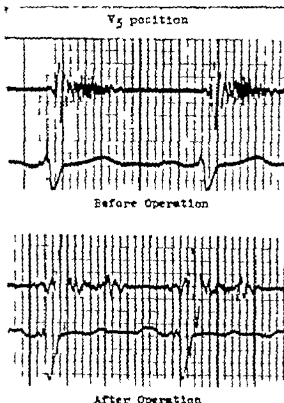


Fig. 5. Case II. Phonocardiograms.

gram remained essentially unchanged. The chest x-ray film after the operation revealed no appreciable change in the size of the heart.

The patient returned to Florida and personal follow-up has been impossible. However, direct communication with the patient 1 year after operation indicates that he has no symptoms referable to his heart other than slight dyspnea on exertion. Direct communication with the Veterans Administration Hospital, Bay Pines, Florida, where the patient is being followed on an outpatient basis, indicates that with digitoxin and diuretics he has remained fairly well compensated. One year after operation the chest x-ray film and electrocardiogram remain essentially unchanged.

Comment

Again the systolic murmur and thrill at the aortic and mitral valves with hemodynamic findings and cineangiographic studies indicating mitral insufficiency suggested that the murmur actually was originating at the mitral valve. Inasmuch as it was mimicking aortic stenosis the possibility of rupture of the chordae tendineae to the posterior leaflet of the mitral valve was considered and was proved to be correct at time of operation.

The left atrial enlargement noted at operation was striking and has been observed by others.[11] The exact pathogenesis of the giant left atrium is not clear but Rogers and Wittels[12] suggested that it might result from a high-speed regurgitant jet causing post-stenotic dilatation in reverse. Possibly cardiac fluoroscopy in the present 2 cases might have revealed a brisk systolic expansion of the left atria which might have been of help in distinguishing mitral insufficiency from aortic stenosis.[13]

Discussion

The initial impression was that both of these patients had aortic stenosis in view of the systolic murmur and palpable thrill in the second right intercostal space. Cardiac catheterization and cineangiography, however, indicated mitral insufficiency.

The absence of a significant gradient across the aortic valve would indicate that the murmur and thrill noted to the right of the sternum did originate at the mitral valve. The most plausible explanation for the production of the murmur is that of Osmundson and associates,[1] who postulated that the regurgitant stream of blood strikes the left atrial wall in close approximation to the aortic valves, producing the murmur and thrill in the aortic area. A jet lesion in the wall of the left atrium was reported by them and by others.

The etiology of the ruptured chordae tendineae in these 2 patients could not be determined. Various causes have been recognized including bacterial endocarditis, rheumatic valvular disease, and trauma.[2]

In view of the recent advances in surgical techniques for the repair or replacement of the mitral valve, the diagnosis assumes increasing importance. In a recent review of 6 cases, Menges and associates[11] stressed the fact that the collection of 6 cases in 18 months was due to advances in cardiovascular surgery and the recognition of this entity at the operating table.

Summary

Two cases of mitral insufficiency mimicking aortic stenosis, due to ruptured chordae tendineae to the posterior leaflet of

the mitral valve are presented in one surgical repair was successful In both the diagnosis of aortic stenosis was entertained prior to appropriate cardiac catheterization and cineangiographic studies.

Cardiac catheterization was performed by Dr R. L. Raley City of Memphis Hospitals, University of Tennessee, Memphis, Tenn. Surgery was performed by Dr James W Pate, Associate Professor Thoracic Surgery University of Tennessee, and Consultant in Thoracic Surgery Veterans Administration Hospital, Memphis, Tenn.

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Bleeding during oral anticoagulant therapy

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It seems to be appropriate to recall that the use of prothrombin-depressing agents in man stems from the fact that Dicumarol produces a severe bleeding disorder in cattle.[1] The isolation of 3,3'-methylenebis (4-hydroxycoumarin) (Dicumarol) by Link and colleagues[2] in 1939 as the causative agent in Schofield's sweet clover disease ushered in the era of oral anticoagulant therapy. The fact that Quick already had devised a simplified method for detecting the coagulation defect induced by this agent and had noted that the associated hemorrhagic disorder could be related to the severity of this deficiency[3] encouraged prompt trial of Dicumarol as an antithrombotic agent in man. After preliminary investigation in dogs,[4] Meyer and associates[5] studied responses in 50 patients and urged that the minimal effective dose be employed. Nevertheless bleeding was frequent in early clinical trials with this drug.[6,7] By 1949, Duff[8] was able to find 21 reported fatalities from hemorrhage induced by Dicumarol and added 2 cases to that number.

In spite of the accumulation of a vast experience with oral anticoagulant therapy, hemorrhage continues to complicate its usage. As emphasized by Peyman,[9] the frequency of bleeding has probably diminished as familiarity with these agents has increased over the years, but even in the most recent reports, hemorrhage continues to be a common problem.[10] Review of a number of studies on hospitalized patients[11-13] indicates that bleeding occurs in approximately 10 per cent of cases. Hemorrhage is even more common in ambulatory patients,[9,14-18] affecting 1 of every 3 so treated in this country and England. However, these episodes are largely minor and fatalities are rare. The percentage of bleeding is higher among outpatients, primarily because the protracted nature of the treatment puts the subject at risk over a longer period of time, but also because the intensity of supervision by the physician is diminished. Diet habits, consumption of drugs, general health, and blood prothrombin activity cannot be as carefully controlled as is possible during hospitalization.

Clinical picture

Newcomb and associates[19] have emphasized the diffuse nature of bleeding produced by the indirect anticoagulants in contrast to the focal "blow-outs" observed in patients with hemophilia, whereas Owren[20] has been impressed by similarities between the bleeding of patients with

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Christmas disease and that of patients receiving anticoagulant therapy. In our experience, severe overdosage produces a diffuse hemorrhagic disorder dominated by hematuria, gastrointestinal bleeding, and wound oozing, but the most common single source of bleeding is the urinary tract. Hematuria was the primary clinical problem in approximately 40 per cent of 130 hemorrhagic episodes observed at the University of Michigan Medical Center from 1947 to 1960. The appearance of blood in the urine was usually heralded by unilateral and sometimes bilateral flank pain. Diagnostic problems occasionally ensued when pain preceded the detection of gross hemorrhage by as much as 12 hours, especially when the pain was atypical in location. The point of bleeding was often found to be in the lower urinary tract when hematuria occurred in the absence of flank pain. In recent years reports of atypical sites of bleeding in the absence of a generalized hemorrhagic diathesis have appeared. Some of the critical areas affected have been the brain,[21] wall of the bowel,[22] ovary,[23] and adrenal glands.[24] These unusual types of hemorrhage are rare, and fortunately so, since they are frequently fatal.

Cause

Spontaneous hemorrhage occurs, in general, because of disturbances in platelet activity, plasma coagulation factors, or vascular integrity. It is well known that the coumarin and indanedione drugs impair coagulation, so that it is not surprising that bleeding during the administration of these agents has been attributed to this effect. In 1947 Allen and associates[11] reported that hemorrhage was rare when the "prothrombin activity" was above 10 per cent. It soon became apparent, however, that the coagulation defect produced by these agents was more complex than had originally been supposed. We now know that factors involved in both the first and second stages of coagulation are affected. Specifically, depressions of factors II (prothrombin),[25] VII (proconvertin),[26] IX (Christmas),[27] and X (Stuart Prower)[28] have been demonstrated. Also, it has become apparent with widespread anticoagulant therapy that hemorrhage can occur with prothrombin activity well above 10 per cent as determined by modifications of Quick's test. Because of this and the fact that determinations of prothrombin time do not reflect concentrations of all the factors influenced by oral anticoagulants, efforts have been made to correlate bleeding with levels of individual clotting factors. In fact, good correlations have been reported for factors II,[29] VII,[30] and IX.[29,31] Most recently, Owren has placed heavy emphasis on the importance of factor X. Utilizing the "Thrombotest," which is particularly sensitive to depression of factor X during chronic anticoagulant therapy, he has reported the virtual elimination of bleeding in a large clinical experience by keeping values above 10 per cent.[32] On the other hand, Rodman[33] could not confirm the value of assay of factor II, and Rapaport[34] demonstrated that levels of factor IX are never dangerously depressed when prothrombin concentration by the Quick method is 20 per cent or greater. More recently, Loeliger and associates[35] have found that factors II, VII, IX, and X are comparably depressed by the chronic administration of anticoagulants, and Baugh[36] has observed that levels of factors II, VII, IX, and X are no different in patients with prolonged prothrombin times who are bleeding than in subjects with similar prothrombin times who are not.

Bleeding with prothrombin activity at "safe" levels might be due to the additive effect of a latent disturbance in platelet or vascular function, since Jaques[37] has demonstrated in rats treated with Dicumarol that hemorrhage does not appear unless more than one hemostatic mechanism is impaired. The fact that petechiae occur[13,38] in some patients receiving oral anticoagulants suggests that platelet vascular factors may play a role in the production of bleeding during therapy. Spooner[39] found no decrease in the number of platelets during prolonged Dicumarol therapy in man, but she did demonstrate a decrease in the adhesiveness of platelets. Prolonged survival of platelets has been found by Murphy[40] to accompany decreased stickiness of platelets during intensive anticoagulant therapy. There is no evidence, however, that these changes in platelet

function play a primary role in anticoagulant-induced hemorrhage. Peyman[8] has reviewed the evidence indicating that hemorrhage during Dicumarol therapy is related to the production of a vascular defect; however, in his clinical study he found no convincing correlation between bleeding and tests of capillary fragility.

In our own experience,[42] bleeding usually occurs in association with excessively depressed prothrombin activity as determined by the Quick test (values of 15 per cent or below), and previously unrecognized organic lesions are usually the cause of bleeding which starts at higher prothrombin levels. We have found that the major causes of bleeding during oral anticoagulant therapy lie in the realms of judgment on the part of the physician, laboratory technique, and the cooperation of the patient. These practical aspects of the use of prothrombin-depressing agents are carefully outlined by Duff.[42] Amplification of the problems encountered in one-stage prothrombin estimations and particularly the pitfalls in the use of various thromboplastins and the construction of prothrombin activity curves can be found in the study of Rodman and associates.[34] Occasionally, bleeding occurs in association with sharp and unexpected declines in prothrombin activity, and patient, laboratory, and physician are all above reproach. Such complications are often related to additional medication which has increased the sensitivity to the oral anticoagulant. The list of drugs which can do this is lengthening steadily; it includes aspirin,[43] phenylbutazone,[44] tetracycline and streptomycin,[36] D-thyroxine,[7] ethyl chlorophenoxyisobutyrate,[4] and methandrostenolone.[45]

Treatment

Oil-soluble vitamin K_1 specifically counteracts the coagulation defect produced by coumarins and indanediones, and its availability has minimized the hazard of anticoagulant overdosage. The main problem with the use of this antidote is the selection of the dose to be given in specific circumstances. In early clinical trials with vitamin K_1, huge intravenous doses ranging from 500 to 1,000 mg. were used.[46,47] It soon became apparent, however, that considerably smaller doses could be equally effective.[48] Subsequently, various authorities[49-52,54] have pointed out the potency of as little as 2.5 mg. of vitamin K_1 given intravenously or by mouth. The study of Rehbein and associates[47] demonstrated quite well that even in dire circumstances the administration of more than 50 mg. intravenously was superfluous if not hazardous. There are two reasons why it is desirable to administer the *minimum* effective dose. The one, which is well documented, is the development of resistance to subsequent oral anticoagulant therapy after excessive K_1.[53,48] The other, which is not confirmed, is the development of rebound hypercoagulability, although the study of Sise[17] suggests that such a phenomenon may appear when prothrombin depression is reversed after a hemorrhagic episode. As opposed to the relatively inactive water-soluble vitamin K preparations, vitamin K_1 emulsion given intravenously produces its beneficial effects in 4 to 8 hours.[46,53] For this reason it is rarely necessary to utilize any other form of therapy in the bleeding patient. If the situation is desperate, an immediate correction of the clotting factor deficiencies can be obtained by infusing whole blood, plasma, lyophilized plasma, or a plasma fraction rich in clotting factors.[56] In general, the selection of the amount of K_1 to be used and the choice of the route of administration is based on four factors: severity of hemorrhage, duration of prior treatment, severity of prothrombin depression, and the desirability of resuming therapy. Life-threatening bleeding demands the use of intravenous K_1 in maximal dosage (50 mg.). Mild hematuria in a patient during the first week of therapy responds to less K_1 than similar bleeding in the patient on long-term treatment. Hemorrhage with prothrombin time in excess of 60 seconds requires more K_1 than does the same problem occurring with less depression of prothrombin activity. If therapy is not to be continued after treatment of the bleeding episode, larger amounts of K_1 may be used than if the anticoagulant program is to be reinstituted. In general, 15 to 25 mg. of K_1 is adequate to bring prothrombin activity back up to safe levels in patients with the usual mild anticoagulant-induced hemorrhage.

Prevention

A carefully selected adequately in formed cooperative patient who is being followed closely by an experienced phy sician with the aid of properly trained laboratory personnel is the right combi nation for "safe" anticoagulant therapy Most severe bleeding problems can be eliminated by adherence to that formula *if the therapeutic goal is kept within reason able limits* It must be recognized that Owren s P & P test and Thrombotest are in general, more sensitive to the effects of coumarin drugs than the Quick test so that a 10 to 20 per cent range with the former tests is equivalent to a 20 to 40 per cent range with the latter [21, 22, 44] This being the case the danger level will de pend on which test is being used With the Thrombotest this level has been found to be at about 10 per cent activity This suggests that the safe range with the Quick test lies above 20 per cent activity It is doubtful whether the one test is superior to the other if this difference is kept in mind. In our experience in the absence of focal vascular weakness, hemorrhage is rare at prothrombin concentrations greater than 20 per cent by the Quick test Although there is some evidence from studies on hospitalized patients that more intensive therapy has a greater antithrom botic potential [11, 44] a recent, limited study of this problem among ambulatory pa tients[42] suggests that optimal results are obtained with Quick test values of 30 to 50 per cent. In the absence of further in formation relating efficacy of therapy to Quick test levels, it would appear that the lower end of the therapeutic range in out patients followed with this test should not be under 20 per cent.

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Fundamentals of clinical cardiology

Cardiac catheterization

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When Forssmann demonstrated the feasibility of cardiac catheterization by catheterizing his own heart and Cournand with Richards showed that this procedure could provide previously unobtainable physiologic data, a new era in medicine was initiated. Eventually, techniques were developed for catheterization of all the cardiac chambers (Table I).[1-9] The purpose of this discussion is to review the role that cardiac catheterization has played and will play in clinical cardiology. In addition, we wish to summarize some of the past experience gained in the medical and pediatric cardiovascular laboratories of one institution.

The development of cardiac catheterization as a diagnostic tool, encouraged by rapid strides in cardiac surgery, has changed the complexion of clinical cardiology in many ways. Congenital heart disease incompletely diagnosed is no longer an acceptable diagnosis. Awareness of the incidence of certain forms of congenital heart disease has risen precipitously. Today, it is difficult to believe that as late as 1949 Greene and associates[10] could find only 68 autopsy proved cases of pure pulmonary stenosis in the world literature or that as recently as 1947 Taussig[11] stated that she had not had an opportunity to study a single proved case of pure pulmonary stenosis. It is now apparent that this malformation accounts for 10 to 14 per cent of all forms of congenital heart disease.[12]

The opportunity provided by cardiac catheterization to correlate clinical signs with hemodynamic events and anatomic variations has enabled the clinical recognition and quantitation of complex cardiac lesions. In addition, previously unrecognized forms of heart disease have been discovered and defined with catheterization techniques. Hypertrophic subaortic stenosis provides a prime example of such a phenomenon. Today, a diagnosis of hypertrophic subaortic stenosis may be made utilizing clinical information alone, whereas the disease was unheard of 8 years ago. A recent review by Braunwald and his associates[13] scores the rapidity with which the spectrum of this disease has been elucidated by catheterization techniques.

Physiologic and pharmacologic maneuvers during cardiac catheterization have not only enhanced our knowledge of man's hemodynamic reactions to stress, but have

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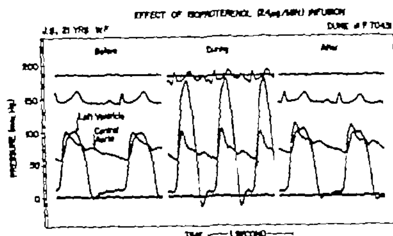


Fig. 1 Hemodynamic response of a patient with latent hypertrophic subaortic stenosis to an infusion of isoproterenol. This patient was the sister of a patient with overt hypertrophic subaortic stenosis. Note that before infusion of isoproterenol there is little if any difference between the systolic pressure in the central aorta and that in the left ventricle. During the infusion of isoproterenol a systolic gradient of 85 mm. Hg develops.

Table I. Milestones in cardiac catheterization

Year	Investigator	Event
1929	Forssmann[1]	First catheterization of human beings
1941	Cournand and Ranges[2]	First series of studies in human beings
1948	Hellems et al.	Described pulmonary capillary pressure
1950	Zimmerman et al.[3]	Retrograde LV technique
1952	Facquet et al.[4]	Transbronchial LV technique
1953	Björk et al.	Percutaneous LA technique
1956	Brock et al.	Percutaneous LV technique
1959	Ross et al. Cope[5]	Transseptal LA technique

also served to unearth evidence of heart disease which was not apparent during basal conditions. Normal resting atrial and/or ventricular pressures may become markedly elevated during exercise in the presence of stenotic valvular lesions. A large gradient across the outflow tract of the left ventricle may be induced in minutes by a small infusion of isoproterenol in the patient with latent hypertrophic subaortic stenosis (Fig. 1).

One of the major benefits accruing from the development of this technique has been the opportunity to demonstrate the innocence of certain murmurs. Many adults who formerly might have been limited in their activity now lead normal lives unhampered by the fear that a functional murmur indicates heart disease.

Indications for cardiac catheterization

There can be no universal list of indications for cardiac catheterization. Each institution will define its own criteria depending upon the skills, needs, and past experience of its staff. The accuracy with which the nature and severity of certain lesions can be defined by clinical and laboratory tools short of catheterization may eliminate the need for catheterization in large numbers of patients. Since catheterization carries a low risk in experienced hands, and since we feel responsible not only for the diagnosis in the individual patient but also for the further definition of the hemodynamic picture in a wide spectrum of diseases, our criteria for catheterization are broad. In this center

patients who are considered to be possible candidates for cardiac surgery are candidates for catheterization and the majority of these patients will undergo catheterization eventually. Adherence to this policy has served to forewarn the surgeon of unsuspected lesions, and to hasten or postpone operation in the equivocal clinical situation. It has also provided a clearer understanding of the natural history of various forms of heart disease.

There are certain clinical situations in which cardiac catheterization is routinely performed. In general all adult patients who will undergo cardiopulmonary bypass for the correction of congenital lesions will undergo a cardiac catheterization. Infrequently exceptions will be made in classic cases of pure pulmonary valvular stenosis. Patients with clinically uncomplicated atrial septal defects do not routinely undergo full-dress cardiac catheterization but the presence of a shunt at the atrial level is demonstrated by utilizing the platinum-electrode and hydrogen inhalation technique described by Vogel and his co-workers.[14]

Almost all adult patients with acquired heart disease scheduled to undergo cardiopulmonary bypass are studied in order to quantitate the severity of the lesion, to rule out the coexistence of unsuspected lesions and to establish a base line in the event that a postsurgical catheterization should appear to be indicated. Because the persistence of murmurs after mitral valvulotomy frequently makes it difficult to adequately assess the status of the mitral valve in patients whose symptoms have recurred after operation, these patients routinely undergo cardiac catheterization.

There are certain less common indications for catheterization in selected adult patients. Cardiac catheterization may provide data that alleviates the anxiety associated with the presence of a murmur of unknown etiology. Catheterization may significantly alter life-insurance rates, workmen's compensation rulings, and decisions concerning employment. Although these are not strictly medical indications, they are taken into account when a decision is made to catheterize a patient.

In children, catheterization rarely is conducted except in the presence of overt cardiac abnormalities with evidence of hemodynamic disturbances. Children with functional murmurs and hemodynamically benign lesions seldom require such procedures. In the majority of these patients, clinical management involves periodic examinations, with the emphasis that parental supervision should be as normal as possible. In the pediatric patient, as in the adult, there is a trend to forego catheterization if there is clinical evidence of an uncomplicated atrial septal defect or pure valvular pulmonary stenosis. Catheterization is not necessarily indicated in the patient with a large ventricular septal defect without evidence of pulmonary hypertension. However, patients with left-to-right shunts and evidence of pulmonary hypertension usually require catheterization in order to document the status of the pulmonary vascular resistance, as well as to rule out an associated defect, such as a patent ductus arteriosus.

Catheterization is mandatory in infants with congestive heart failure secondary to left-to-right shunts. Clinical evaluation alone is frequently not precise enough to clarify the complete diagnosis in this group. Advances in definitive and palliative surgical procedures in this age group continue to place increasing demands upon the cardiologist for a *complete* diagnosis.

There are several clinical situations in which catheterization is definitely indicated not so much to determine the diagnosis but rather to clarify the degree and specific type of anatomic abnormality which is present. In infants suspected of having pulmonary atresia, it is important to determine the size of the right ventricular chamber and to outline the location of the site of obstruction so that the most appropriate palliative surgical procedure may be planned. In truncus arteriosus, the site of origin of the pulmonary arteries must be delineated, since banding of the main pulmonary trunk in a Type I truncus arteriosus may serve to control the congestive heart failure which is secondary to the large pulmonary blood flow. When clinical evidence may indicate the presence of a single ventricle, cardiac catheterization and selective angiocardiography are indicated in order to demonstrate the presence or absence of a ventricular sep-

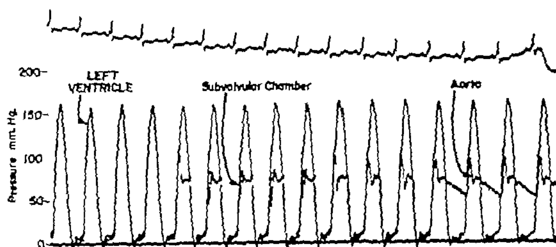


Fig. 2. Pressure tracings obtained from the asymptomatic daughter of a patient with overt hypertrophic subaortic stenosis. Initially, two catheters were placed in the left ventricle; one has been left in the ventricle to continuously monitor left ventricular pressure, whereas the *other* catheter has been withdrawn from the apex to the aorta. Note that there is a systolic gradient between the left ventricle and the subvalvular chamber but no systolic gradient between the subvalvular chamber and the aorta.

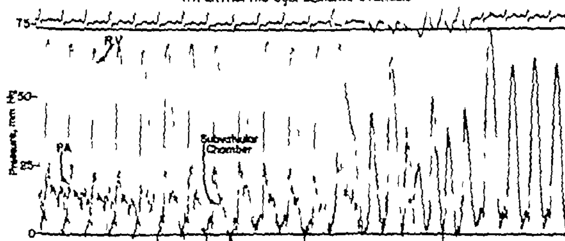


Fig. 3. Pressure tracing obtained in the right side of the heart of the same patient described in Fig. 2. One catheter has been placed in the main portion of the right ventricle (*RV*) to continuously record ventricular pressure. A second catheter has been placed in the pulmonary artery (*PA*) and withdrawn through a subvalvular chamber to the main portion of the right ventricle. Thus this patient had combined hypertrophic subaortic and subpulmonic stenosis.

tum The patient with evidence of congenital heart disease and malrotation of the heart (dextrocardia or dextroversion) frequently presents a difficult diagnostic problem On occasion the underlying anatomic and physiologic defects may be amenable to surgical correction Preoperative clarification of the position of the venous structures is especially useful in planning the most appropriate perfusion procedure

The cardiac catheterization laboratory and catheterization techniques

Since the purpose of cardiac catheterization is to define precisely the physiologic and anatomic status of the heart equipment and techniques to meet this goal must be available in the laboratory There must be adequate means of measuring pressure, flow sound and electrical events within the heart as well as a means of recording visually the anatomic status of the heart In some cases the diagnosis will rest solely or predominantly on one parameter whereas in other cases all the physiologic data available from measurements of pressure and flow as well as anatomic information provided by angiography may be required to define the diagnosis. Figs. 2 and 3 illustrate the classic pressure recordings from a patient with combined hypertrophic subaortic and subpulmonic stenosis little else is needed to make the diagnosis in this case Fig 4 illustrates the usefulness of the simultaneous recording of the intracardiac pressure and electrocardiogram in the patient with Ebstein s anomaly

Fig 5 demonstrates that cardiac catheterization has changed a great deal since the day that Forssmann placed a catheter in his heart and walked upstairs to the x-ray suite to determine the position of the catheter The speed and safety with which cardiac catheterization can be conducted is increased immeasurably by the use of modern image-intensification equipment. Television monitoring during fluoroscopy has many virtues. The study can be carried out in a minimally darkened room thus allaying anxiety in the patient and allowing ease of movement of personnel about the laboratory The visibility of the image to all those in the room allows for

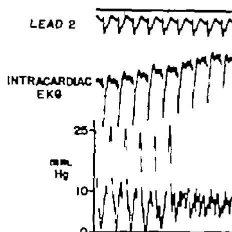


Fig 4 Simultaneous intracardiac pressure and ECG tracings obtained with an electrode catheter in a patient with Ebstein s anomaly Note that a right ventricular type of intracardiac ECG persists, despite the fact that the pressure tracings indicate that the catheter has been withdrawn from the right ventricle to the right atrium This is pathognomonic of Ebstein s anomaly

teaching and advice in movement of the catheter The supporting personnel can keep abreast of the progress of the catheterization by watching the position of the catheter on television

Angiographic visualization is considered to be an integral part of cardiac catheterization It both complements and supplements information gained from physiologic techniques Because of the advantages of depicting motion and the speed with which cineangiographic examinations can be conducted we have used cineangiography as our primary means of visualization We have found that it is useful to combine the recording of changing physiologic events and anatomic relationships on the cineangiographic film[14] (Fig 6) Tape-recording of the televised image allows for immediate playback of any angiographic study This gives almost immediate evidence of the adequacy of the study and frequently decreases the number of injections of contrast medium

The amount and direction of blood flow can be determined by several indicator dilution techniques. In our laboratories the output of both ventricles is determined by either the Fick method or indocyanine-green indicator-dilution techniques.[15] Appropriate sampling of blood within the

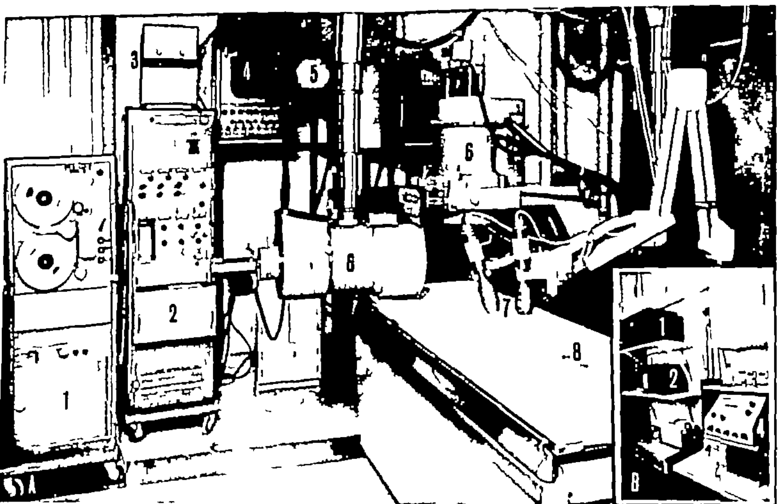


Fig. 5 The modern cardiac catheter laboratory contains much of the equipment seen here in the Duke Pediatric Catheter Laboratory: *1* Tape recorder. *2* Amplifiers and recorder. *3* Count rate meters for isotope-dilution techniques. *4* Oscilloscope for display of physiologic tracings. *5* Television monitor for fluoroscopy and angiography. *6* Biplane cinefluorography unit. *7* Scintillation detectors for isotope techniques. *8* Pressure transducers. The insert illustrates equipment utilized to obtain hemoglobin saturation (*1*, *2*), indicator-dilution curves (*3*), and blood pH and gas determinations (*4*).



Fig. 6. Individual frames from a 35-mm. cineangiogram obtained during the simultaneous injection of contrast medium into the aortic root and the descending thoracic aorta below a coarctation (indicated by the arrows). The pulmonary arterial pressure is simultaneously recorded in the right lower quadrant of each cineangiographic frame. Panel A is during diastole; panel B during systole.

heart will indicate the location of intracardiac shunts. *Although differences in* blood oxygen content may indicate the location of a shunt, we have found that indicator-dilution techniques are more effective in demonstrating small shunts. The injection of an indicator, such as green dye, into one chamber while continuously sampling blood from another chamber, as illustrated in Fig. 7, has provided extremely reliable data concerning shunts and valvular regurgitation. The same principles can be applied to an indicator-sensing system

SELECTED INDICATOR DILUTION CURVES IN COMBINED ASD, VSD, PDA

INJECTION SITE	SAMPLING SITE	INTERPRETATION	CONTOUR
PA, RA, RV	PERIPHERAL ART.	L → R SHUNT	
LV	RV	L → R SHUNT	
LA	RA	NO SHUNT	
Ao	PA	L → R SHUNT	
PERIPHERAL VEIN	SVC, IVC	NO SHUNT	
PERIPHERAL VEIN	RA	L → R SHUNT	



Fig. 7. Group of indicator-dilution curves that would be obtained in a patient with combined atrial (*ASD*) and ventricular (*VSD*) septal defects, as well as a patent ductus arteriosus (*PDA*). Injection into any part of the right heart indicates a left-to-right shunt of unknown location. The early appearance of indicator in the pulmonary artery (*PA*) after injection into the aorta (*Ao*) indicates a PDA. Early appearance of indicator in the right ventricle (*RV*) after injection into the left ventricle (*LV*) indicates a VSD. Early recirculation of indicator in the right atrium after a peripheral venous injection indicates ASD.

utilizing ascorbic acid or hydrogenated saline with a platinum-electrode catheter. This eliminates the need for the withdrawal of blood.

Because of the clear evidence of the course of the circulation, as well as the facility and speed with which data can be recorded, radioisotope-dilution curves have been very useful in severely ill small infants. The technique involves the placement of narrow collimated scintillation detectors over the right lung, the heart, and/or a peripheral body site (usually the head) for monitoring changing radioactivity after selective injections of sodium iodohippurate.[17] Fig. 8 demonstrates the application of this method for the localization of the site of a left-to-right shunt.

The technical approaches to the child and to the adult are frequently similar, but there are significant differences dictated by the size of the patient and the diagnosis suspected. In the adult, most catheters are introduced percutaneously, whereas this approach is seldom used in

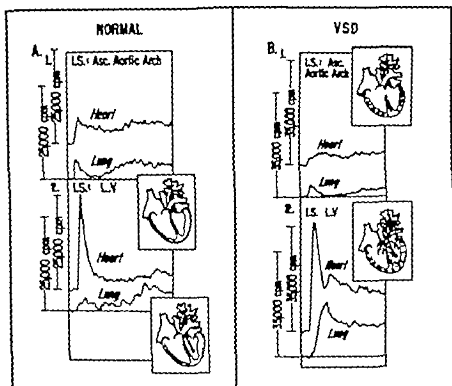


Fig. 2. Use of radioisotope-dilution curves for localizing the site of left-to-right shunt. *Panel A.* Normal curves after injection into the ascending aorta (*1*) and left ventricle (*2*) indicate a rapid washout of the indicator from the heart and great vessels. Only slight activity is recorded after injection into the ascending aorta. *Panel B.* Demonstration of the left-to-right shunt and its location are shown after injection into the ascending aorta and the left ventricle. Curves obtained after injection into the aorta are normal. After the rapid washout of indicator from the left ventricle there is an immediate abnormal increase in activity over the right lung. The heart curve shows abnormal early circulation due to the left-to-right shunt. The normal curves obtained above the aortic valve, coupled with the left-to-right shunt demonstrated by left ventricular injection, indicate the presence of ventricular septal defect (*VSD*).

the child. The right heart can be catheterized from the femoral or antecubital veins in both the adult and the child. The left ventricle can routinely be entered with the retrograde aortic approach if the aortic valve is normal. If in the presence of aortic stenosis, the aortic valve cannot be crossed, the left ventricle can be entered either by passing a transseptal left atrial catheter across the mitral valve or by means of percutaneous left ventricular puncture. Although the introduction of a previously placed left atrial transseptal catheter into the left ventricle allows prolonged study of the left ventricle with minimal discomfort to the patient, we have become less enthusiastic about this approach in cases of aortic stenosis because of the danger of puncturing the dilated aortic root during the attempt to carry out the transseptal catheterization. At the present time, if there is any suggestion of difficulty in placing the transseptal needle in the fossa ovalis prior to the septal puncture in the patient with a dilated aortic root, attempts at transseptal catheterization are stopped and a percutaneous ventricular puncture is performed.

Previous experience in this and other centers has indicated that the transbronchial approach to the left atrium is too uncomfortable for prolonged studies, the percutaneous approach through the back is too dangerous, and the transseptal technique is the most desirable method for the study of the left atrium. However, use of the transseptal technique is not without a risk of morbidity and mortality. We believe that the placement of catheters in the aortic root and across the tricuspid valv

prior to the transseptal puncture provides valuable landmarks which lessen the dangers inherent in this technique Furthermore this technique should not be delegated to an inexperienced person

Cardiac catheterization and the future

Lessons learned from previous catheterizations have eliminated the need for such studies in certain clinical situations. However it is unlikely that the need for cardiac catheterization will be completely eliminated in the foreseeable future There undoubtedly will be changes in technique and the definition of new goals.

Much of the information now collected during catheterization in analog form and later laboriously converted to digital data will be recorded and displayed immediately in digital form Once in digital form such data can be processed by high-speed digital computers operating on line from the catheter laboratory Thus, it will be possible to record pressure pulses from each cardiac chamber convert these pulses to digital form perform numerous mathematical operations on the data correlate the results with cases studied previously in the particular laboratory and display the answer in the laboratory in a matter of seconds. Ventricular pressure volume loops, which are now available only after hours of calculation can be displayed after their rapid derivation from measurements of ventricular pressure pulses and ventricular volume Such measurements of volume may be obtained by extension of roentgen videodensitometry techniques.[18]

The catheterization procedure itself may well be simplified by modification and miniaturization of the equipment that is presently available In the near future catheters should be developed which are extremely small in diameter limber enough to be flow guided and yet contain multiple sensing devices at the catheter tip Such catheters would be capable of monitoring the intracardiac electrocardiogram pressure, sound hemoglobin saturation and the concentration of certain indicators. Since the catheter would be flow guided and capable of sensing changes in intracardiac ECG and pressure a complete right heart catheterization could be carried out while the patient is in the outpatient clinic, in much the same fashion that hydrogen indicator curves are obtained today [14] The addition of telemetry to this form of small multisensing catheter may allow the long term study of intracardiac phenomena in patients during normal daily activity

Other innovations are on the immediate horizon Fiber-optic techniques offer a host of new possibilities. A fiber-optic system can be mounted in a catheter and used to document rapid fluctuations in hemoglobin saturation as well as indocyanine-dye concentration within the heart Preliminary experiences with special fiber-optic catheters indicate that intracardiac structures, such as valves can be visualized directly In the future the surgeon may well be able to review a motion picture demonstrating the anatomy and function of the particular valve to be repaired This will also allow a more precise understanding of normal valve function which in turn may lead to the design of more efficient and durable artificial valves

Further development of lasers may provide excellent light sources for fiber-optic systems. The laser may also be used for intracardiac surgery via fiber-optic devices. It is conceivable that stenotic valves which can be visualized with a fiber-optic catheter can also be opened by a laser beam directed through a fiber-optic catheter

Improvement in angiographic equipment and techniques are in the immediate offing More efficient generators, higher resolution image intensifier tubes, stereocineangiographic techniques, and biplane cineangiography are now in active use in several laboratories in this country The more conventional means of documenting the structure of the heart will be supplemented by other advanced techniques such as ultrasonics. Preliminary studies have already demonstrated the usefulness of this technique in the evaluation of mitral valve disease [19]

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Prevention of subacute bacterial endocarditis associated with dental procedures

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Because of its frequent onset after dental manipulations, bacterial endocarditis is well known to dentists. The recommendations of the American Heart Association for prevention of this disease are available to members of the dental profession. Current practice, however, appears to fall short of its objective in view of recently observed data.

Current practice. From 50 to 80 per cent of patients have bacteremia during dental extractions or extensive dental procedures, especially in the presence of badly infected gums. The most common organism noted and the organism which causes the overwhelming majority of cases of subacute bacterial endocarditis is *Streptococcus viridans*.[1] The recommendations of the American Heart Association to prevent septicemia due to the alpha streptococcus (*Streptococcus viridans*) and the resultant bacterial endocarditis are as follows: The administration of penicillin for several days before the procedure is optional on the part of the physician. On the day of surgery, 500,000 units of buffered penicillin G or phenoxymethyl penicillin is to be given orally 4 times daily and continued for 2 days after surgery. An alternative is to give an intramuscular injection of 600,000 units of procaine penicillin supplemented by 600,000 units of crystalline penicillin 1 to 2 hours before the procedure. For 2 days postoperatively, 600,000 units of procaine penicillin are given intramuscularly. If the patient is allergic to penicillin, erythromycin is to be used.

Comment and review of literature. This appears to be a reasonable approach to prophylaxis if the alpha streptococcus is sensitive to penicillin. However, it has been demonstrated that treatment with penicillin can definitely alter the bacterial flora of the mouth and promote the emergence of gram-negative organisms as well as penicillin-resistant alpha streptococci.

Garrod and Waterworth[2] reported 2 cases of bacterial endocarditis due to penicillin-resistant alpha streptococci in which dental extraction was preceded by prophylactic penicillin therapy. They also noted that in 31 patients on penicillin prophylaxis for rheumatic fever, the vast majority of strains of *Streptococcus viridans* isolated from the saliva were resistant to penicillin. They further observed in 2 normal adults given phenoxymethyl penicillin, 250 mg. 4 times daily, that a population of resistant alpha streptococci was

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established within 48 hours. When penicillin was stopped, sensitive alpha streptococci usually disappeared after 2 days.

Recently, Naiman and Barrow[3] cultured the anterior gum tooth margin and the posterior pharynx in 21 children receiving penicillin prophylaxis for rheumatic fever, and penicillin-resistant alpha streptococci were found in 81 per cent of the cases studied. Of the organisms normally recovered from the mouth, 4.3 per cent are resistant alpha streptococci. Thus, a small resistant population is always present and has the potential to become dominant.

Bacterial endocarditis occurs most frequently in individuals with rheumatic heart disease, congenital heart disease, and syphilitic aortic valvular disease. However, normal valves can also be a site for the development of endocarditis, especially in the elderly.

Anderson[4] in studying the clinical features of 14 patients over 60 years of age who developed bacterial endocarditis found that in only 2 patients was there any known antecedent valvular disease. Thus, the disease can occur in patients not expected to become affected and may run a more insidious clinical course than in younger patients.

Guze and Pearce[5] studied 17 patients who acquired bacterial endocarditis during hospitalization. The median age for this group was 59 years, and the primary illness which prompted hospitalization usually was a condition requiring surgery. Postoperative infections were thought to be etiologically related to the subsequent valvular infection. Here again, endocarditis occurred most frequently on normal valves.

In the experimental animal, many different forms of stress can lead to the formation of bland vegetations on heart valves. Angrist postulated that stress, particularly in the elderly, can lead to the production of nonbacterial endocarditis. When this nidus is contaminated with streptococci from the blood stream, bacterial endocarditis can ensue. Since all patients over the age of 60 are potentially prone to develop bacterial endocarditis when undergoing surgical procedure, it seems to be reasonable that they should also receive prophylactic penicillin. The authors realize that this concept is controversial. Further statistical studies are necessary to determine whether the percentage of cases of bacterial endocarditis found in the elderly after surgery is high enough to warrant a treatment which in itself carries a small risk.

Recommendations. On the basis of the preceding evidence, we now propose a rational plan of therapy to prevent bacterial endocarditis.

All patients with rheumatic heart disease (not on penicillin prophylaxis), syphilitic aortic valvular disease, and congenital heart disease should receive penicillin prophylaxis for bacterial endocarditis at the time of oral surgery, endodontic therapy, tooth extraction, or manipulation of periodontal tissue. (This applies only if the patients are not allergic to penicillin.) (1) One to 2 hours before the procedure they should be given an intramuscular injection of 600 000 units of aqueous procaine penicillin with 600 000 units of aqueous crystalline penicillin. Thereafter, daily for 2 days, they should receive 600 000 units of aqueous procaine penicillin intramuscularly. (2) If patients are on oral penicillin prophylaxis for rheumatic heart disease, the physician should discontinue this medication for 1 week and then institute the parenteral form of prophylaxis. An alternate mode of drug therapy in this group is to give an antibiotic such as erythromycin orally, 250 mg. 4 times daily for 3 days, beginning 6 hours prior to dental extraction or general instrumentation.

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Cerebral embolism

Fragmentation and dissolution of a cerebral embolic plug was originally postulated by Fisher and Adams[1] to explain hemorrhagic embolic cerebral infarction when no embolus is found and a number of recent reports on fragmentation of retinal and cerebral embolic material have further renewed the interest in the subject of cerebral embolism.[2-]

During a recent study of strokes, consecutive patients with unequivocal cerebral embolism were subjected to cerebral angiography within 60 hours of the onset of the ictus, in order to locate the embolus and study its natural behavior. Stringent diagnostic criteria were used which consisted mainly of a very abrupt (almost instantaneous) onset of a stroke in a young person in the presence of a readily identifiable and potential source of embolism; necropsy verification of the diagnoses was also available in many fatal cases. In this study, 17 of the 20 patients revealed an occlusive embolic lesion, whereas a normal cerebral angiogram was found in only 3; the middle cerebral territory was the common site for embolic occlusion (12 cases) and in only 4 patients was the embolic plug arrested in the carotid territory. Such a high incidence (85 per cent) of angiographic lesions in embolic cerebral infarction is quite in contrast to a high incidence (60 per cent) of normal angiograms *obtained in nonembolic cerebral infarction.*

The site of embolic arrest would depend upon the size of the embolic mass. A large embolus is likely to be arrested in the carotid artery, and in these cases an immediate embolectomy before the embolus fragments and migrates to occlude the distal intracranial circulation, is highly recommended. However, the neurovascular syndromes resulting from an acute middle cerebral and a carotid artery lesion are very similar and often difficult to differentiate. Absent superficial temporal pulse and embolic fragments in the retinal vessels on the side of carotid artery embolism *when present* may prove to be very helpful, but in a majority of the cases the embolus is lodged in the distal cervical course and *only* the cerebral angiographic findings aid in the arrival at an accurate diagnosis.[10] Moreover, in the presence of strong conjugate gaze deviation and frequent blepharospasm, reliable measurement *of retinal artery pressures (ophthalmodynamometry)* are difficult *to obtain. With an early* and accurate diagnosis and prompt surgical treatment (carotid embolectomy), severe structural brain damage can be prevented.[10,11]

In this series, the authors also obtained another cerebral angiograph within 100 hours of the first study and found that the embolic plugs had frequently migrated from their previous locations, often were fragmented into smaller masses, and even had disappeared completely so as to restore a normal angiographic pattern. It was observed *that the process of fragmentation and lysis was spontaneous* and in one of their cases, even a 50-hour-old embolic plug could undergo a complete dissolution within 10 minutes.[1] Moreover, the use of greater mechanical force at the time of angiography did not bring about rapid fragmentation or clot lysis. It has been suggested that such spontaneous and rapid lysis (within a few minutes) of an embolic plug which has stayed at a particular locus for more than 24 hours may be governed by (among many unknown factors) the fibrinolytic enzymes present within the blood, the embolus, and the arterial wall.[8]

A higher rate of survival ($p < 0.05$) was also noted in patients in whom the occluded angiographic circulation was restored to normal; the number of angiographs obtained in the alive and the dead groups was almost the same, and there was no significant difference in the number of angiographic lesions in the two groups.[8] From *these observations, it seems that if the embolus* cannot be removed surgically, it should be fragmented and dissolved as early as possible. Whether parenteral or local infusion of fibrinolytic agents would enhance clot lysis, *in vivo*, yet remains to be determined in controlled experiments. Likewise the value of focal ultrasonic beam aimed at the site of arrested embolic plugs needs to be evaluated.

Despite multiple angiographic procedures in this series, the case mortality was not significantly affected, so that a plea is made in favor of early angiography in patients with cerebral embolism.[7,9,10] Only future studies, on larger series, can indicate the right place for angiography in patients with recent cerebral embolism.

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Report of a complication associated with the incorrect use of a Bing-Gadd catheter deflector

A number of techniques and devices have been developed to expedite manipulation of a catheter and direct the tip of the catheter into otherwise inaccessible sites. Such devices may be extremely useful when selectively used but may be associated with complications, especially when misused Such complications may then unfortunately lead to unwarranted rejection of useful tool. The present communication is a description of a complication associated with the improper use of a Bing-Gadd catheter deflector and is intended to alert others to a potential hazard associated with its use

The Bing-Gadd catheter deflector consists of a flat metal strip one and three-eighths inches long attached to the distal end of closely wound stainless steel helical coil A stainless steel monofilament wire of small diameter is ttached to the distal tip of the flat metal spring and is threaded through the helical coil

When traction is pplied to the tensing wire by finger pressure upon the manipulator curvature of the spring tip of the deflector is effected. When intra ascular modification of the curvature of catheter tip is desired, the Bing-Gadd catheter deflector is to be ad anced within the lumen of the catheter to just within the tip, nd traction applied to the tensing wire It is intended that the deflector be used with a specially designed catheter of matched length, so that the tip of the deflector does not extend beyond the tip of the catheter W ha e found that the deflector is a useful adjunct during difficult catheterizations.

Although t is not intended by the designer we ha frequently used the deflector with catheters of arying lengths, relying on isualization by image-intensification fluoroscopy to determine the relationship of the t p of the deflector to that of the catheter Occasionally we have extended the deflector cautiously beyond the tip of the catheter and produced a curv ture of the deflector which could be directed across a alve, and after relaxing the tension of the deflector w ha e then passed the catheter over the deflector to the desired site.

During transeptal left heart catheterization of a patient with hypertrophic subaortic stenosis, antegrade passage of a transeptal No 2 5 Brockenbrough catheter across the mitral alve could not be achieved The catheter had been troduced percutaneously into the right femor l ein In order to control the curvature of the tip, B ng-Gadd catheter deflector was ad anced to the tip of the catheter and traction was pplied to the tensing wire, but the resulting curvature was insufficient to permit manipulation across the mitral valve. The deflector was then ad anced beyond the tip of the catheter but the distance was not sufficient for the tensing wire to clear the lumen of the Brockenbrough catheter When traction was applied to the tensing wire, the radius of curvature of the

*Supplied by the American C stoscope Makers, Inc., Pelham Parkway Pelham Manor N Y

spring steel tip wa[s] shortened placing upon the tip stress for which it was not designed [A]cute and permanent 90-degree angulation of the distal 7 mm of the spring steel resulted as well as breakage of the tensing wire at its distal attachment The bent deflector could not be withdrawn into the catheter the tip of which was across the interatrial septum in the left atrium It was appreciated that the flat spring steel tip which was angulated and protruding from the catheter tip could seriously lacerate the vascular bed A emergency thoracotomy was contemplated However it wa decided to attempt to withdraw the catheter and protruding steel tip cautiously across the interatrial-septal puncture and down the inferior [v]ena [c]av[a] The withdraw[a]l was constantly monitored by image-intensification fluoroscopy Had resistance to withdrawal been encountered the procedure would ha[v]e been abandoned and surgical removal [c]arried out Fortunately withdrawal from the left [a]trium and finally through the percutaneous femoral-vein puncture site wa[s] carried out uneventfully The patient was unaware of the complication

This description of a complication associated with the use a a Bing-Gadd catheter deflector is presented in order to alert others to this potential hazard when the guidewire is extended beyond the tip of the catheter with which it is used. This report should not deter others from the proper use of the catheter deflector as originally described.

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Red cell volume, hypertension, and renal disease

[I]n 1905 Gaisbock described the syndrome poly[c]ythemia hypertonica in which hypertension and polycythemia occurred together with renal [d]isease Certai[n] diseases of the kidney are now known to cause polycythemia the red cell mass returning to normal [a]fter removal of the renal lesion whenever this i[s] possible[4-8] (Fig 1) and it seems to be likely that some patients with Gaisböck's syndrome ha[v]e renal polycythemia with coincident hypertension A more subtle relationship between renal disease, polycythemia and hypertension is suggested by a patient with stenosis of the renal artery i[n] whom polycythemia and hypertension were cured by nephrectomy[9] This result implies that ischemia of renal tissue might sometimes be a common factor in the production of polycythemia and hypertension Moreover it ha[s] been suggested that the juxtaglomerular apparatus, known to produce renin also produces erythropoietin,[10] but the experimental evidence for this is inconclusive.[11] [12] In man stenosis of the renal artery is not often accompanied by polycythemia, and in a patient with hydronephrosis, hypertension, and polycythemia nephrectomy cured the polycythemia without affecting the hypertension[13] Polycythemia may also complicate other hypertensive diseases, such as Cushing's syndrome and pheochromocytoma.[1]

In hypertensive patients, a diagnosis of polycythemia should rest upon measurement of the total red cell volume rather than on hematocrit reading alone unless these are grossly elevated This follows from the fact that both [v]enous hematocrit and whole body hematocrit vary more than normal in uncomplicated essential hypertension When the total red cell [v]olume has been measured, it is necessary to select the parameter to wh[ic]h it should be referred. Usually red cell volume is expressed i[n] relation to body weight but this correlation is poor i[n] normal subject and therefore, unsatisfactory for the detection of small abnormalities A better correlation is found between red cell volume [a]nd total body water [14] Fig 1 shows this relationship in 23 normal subjects [s]tudied by Hyde and Jones, and also illustrates the return to normal values of the red cell volume [a]fter nephrectomy in 4 patient[s] with renal polycythemia whom I have [s]tudied.

When this relationship between red cell volume [a]nd total body w[a]ter was examined in 12 patients with essential hypertension who were free of cardiac [a]nd renal complications, it wa[s] found that only 5 patients had red cell volumes w[i]thin the 95 per cent confidence limit[s] of the predicted value.[11] It is possible that, in hypertensive subjects, total body water varies more than normal in relation to other body parameters and this might explain the greater variation observed This study[1] provided no evidence that either red cell or plasma volume wa[s] systematically increased or decreased in uncomplicated essential hypertension

Reduction in plasma [v]olume may suggest the presence of polycythemia by producing a rise in hematocrit when total red cell v[o]lume is normal In essential hypertension both [v]enous and whole body hematocrit are more variable tha[n] normal[11] and I have studied 3 hypertensive patient[s] in whom the venous hemat[oc]rit was ele[va]ted, but in whom

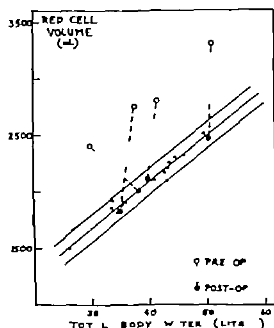


Fig. 1 Relationship between red cell volume and total body water in 23 normal subjects and in 4 patients with renal polycythemia before and after nephrectomy. The regression line with 95 per cent confidence limits is taken from the data of Hyde and Jones (Brit. J. Haemat. 8:283 1962, by permission).

the red cell volumes were normal when referred either to body weight or total body water. In these patients with "relative polycythemia," the primary abnormality appears to be in the regulation of plasma volume, and this subject is under investigation at present.

Perhaps the most dramatic variations in plasma volume encountered in hypertensive disease are those occurring in some patients with pheochromocytoma. In this condition, large changes in venous hematocrit may occur rapidly because of plasma volume alterations.[17] However true polycythemia, with expanded red cell volume, may also be produced by a pheochromocytoma, whereas Brunjes, Johns and Crane[1] described 2 patients with pheochromocytoma in whom red cell volume was low in association with a reduced ratio of whole body hematocrit to venous hematocrit (normal, 0.91). This ratio (WBH/VH) returned to normal in the immediate postoperative period. I have encountered similar reductions in the WBH/VH ratio in 2 patient with pheochromocytoma, but in one case this abnormality persisted when the blood pressure and excretion of vanilmandelic acid were normal 1 month after removal of the tumors (Table I). Moreover similar reductions in the WBH/VH ratio may occur in essential hypertension.[11]

The evidence for abnormal regulation of plasma volume in hypertension is outside the scope of this article, but it seems to be probable that further investigation of the control both of red cell volume and of plasma volume in the various hypertensive diseases would be rewarding.

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Table I. Blood volumes in a patient with bilateral pheochromocytoma before and 1 month after removal of the tumors

	Body weight (Kg.)	Venous hematocrit (%)	Red cell volume (ml.)	Plasma volume (ml.)	Whole body hematocrit / Venous hematocrit	V.M.A. excretion (mg./day)
Before operation	43.64	42.5	960	1,730	0.81	22.5
After operation	43.66	48.0	1,190	1,900	0.80	5.1

V.M.A. 3-Methoxy-4-hydroxymandelic acid (normal range < 7 mg. per day).
Red cell and plasma volumes were measured with ^{51}Cr and ^{131}I-human serum albumin, respectively.

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Abnormal ventricular repolarization in Macaca mulatta*

We have recently observed that 6 per cent of 351 apparently healthy laboratory *Macaca mulatta* show inverted or diphasic T waves in Leads II III and aVF[1] An exploration was carried out in order to determine the effects of changing body position drugs and hyperventilation on the abnormal electrocardiogram The results in 8 experimental animals were contrasted with the findings obtained in 9 control monkeys showing upright T waves in these leads.

The following observations were recorded in the experimental animals (a) There was a great variability in the direction of the T wave when repeated tracings were recorded over a 7-month period (b) There was a tendency for some of the "abnormal" electrocardiograms to become normal over a period of several months. (c) Changing body position produced only minor changes in the T wave pattern and did not return it to normal. (d) The direction of the T wave was modified in the abnormal group of animals by epinephrine sympatholytic and vagolytic agents, as well as general anesthetics and nitroglycerin. (e) Hyperventilation with 100 per cent O_2, as well as with CO_2-O_2 (5 95) either normalized the negative T waves or inverted positive T waves in some of the abnormal animals. Neither procedure inverted upward T waves in control animals. The hyperventilatory changes were not modified by general anesthetics, autonomic blocking drugs, or nitroglycerin. (f) There were no direct proofs that the abnormal electrocardiogram was related to gross disturbance of the central nervous system electrolyte imbalance extracardiac pathology ventricular hypertrophy coronary insufficiency or a diffuse type of myocarditis which is very common in the rhesus monkey

The abnormal electrocardiograms observed in *Macaca mulatta* resemble in some aspects those described in the human being under the influence of fear anxiety[2] or intense emotion and variously referred to as "functional electrocardiogram."[5]

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Book reviews

PEDIATRIC ELECTROCARDIOGRAPHY By Warren G Guntheroth M D Philadelphia, 1965 W B Saunders Company 150 pages Price $7

This is a good book, but unfortunately it is limited to a general discussion of the principles of electrocardiography which may be found in other existing books concerned with adult electrocardiography and therefore contains relatively little in its few pages about pediatric electrocardiography There are important differences between the patterns found in adults and children especially infants and the newborn This book fails to emphasize these differences adequately For example, on page 124 Figure 102 displays a pattern of "anterior myocardial infarction a 3-year-old patient with endocardial fibroelastosis. If this is presented as a characteristic pattern of anterior infarction in children the author should make this clear since no cardiologist would consider this to be characteristic of anterior infarction in adults. Such patterns are encountered in patients with cardiomyopathies and with large left and right ventricles The author may have autopsy evidence to support the reliability of such a pattern and if so, he should make it clear to the reader in future ed tions.

This is a good book for beginners and for those who wish to know Dr Guntheroth concepts of pediatric electrocardiography

MICROFISIOCIRCULATION OBSERVABLE VARIABLES AND THEIR BIOLOGIC CONTROL. By Elio Maggio, M D F I C.A., Springfield, Ill 1965 Charles C Thomas, 194 pages. Price $16.50

This is an English version with modification of the reports made at a conference on the microcirculation held in Galveston in 1954. In 1962 Dr Maggio published "Micro- e macro-emocircolazione, which constitutes the basis for this book. Although Dr Maggio is becoming a American citizen and is n otolaryngologist he continues his interest in the microcirculation which began in Italy

This relatively small book review the history methods, anatomy and physiology biologic control, pathologic response to injury and other aspects of the microcirculation. The book is well illustrated and an atlas is appended, with a fairly good bibliography This book does not present a critical discussion of the present-day knowledge or needs in the field but rather describes briefly that which is known about the microcirculation. The discussions are from the point of view of normal physiology There are few if any discussions of disease or problems in ma The presentations are primarily of f nction microscopy and anatomy The book therefore should be primarily of interest to beginners and students of anatomy and circulatory physiology This elementary book w ll not interest investigators of the circulation but the student of anatomy should find it to be a good source of references on the subject Unfortunately very few references date back more than 10 years. Most of that which is found in this book was known and published during and even before the nineteen thirties and nineteen-forties. However this book continues the present-day practice of not properl presenting medical knowledge in its time sequence in spite of Chapter I on history The accuracy of the historical data is questionable For example, in Chapter I the reader would gather that the biologist who ntroduced the microscopic method to the study of the liv ng microcirculation was Dr Zweifach rather tha the great biologist, Robert Chambers, who trained Zweifach This example reflects contemporary medical writing

THE PRACTICAL MANUAL FOR CLINICAL LABORATORY PROCEDURES and HANDBOOK OF CLINICAL LABORATORY DATA. Edited by Henry C. Damm Ph D Western Reserve University and John W King M.D Ph.D Cleveland Clinic Foundation Cleveland Ohio. Cleveland, 1965 The Chemical Rubber Company 469 pages. Price $25 per set

These two manuals are very good reference books which describe the procedure for performing the common clinical laboratory measurements. The instructions necessary for patients and the procedures are described in detail. Tables of normal values are given. The books are well supported by good bibliographies. These are highly recommended not only to workers in laboratories but students and physicians as well who should know more about the laboratory tests they so freely order

ELECTROCARDIOGRAPHY AND VECTORCARDIOGRAPHY INSTRUMENTATION FUNDAMENTALS, AND CLINICAL APPLICATIONS. By Lawrence E. Lamb M D Professor of I ternal Medicine, USAF School of Aerospace Medicine, Brooks Air Force Base, Tex. Philadelphia 1965 W B Saunders Company 609 pages. Price $17

This is an elementary type of presentation of very complex phenomena. For example, on page 1 the discussions of an tom are so simplified that the uthor fails to mention mesons and other subatomic particles as being parts of an atom. This is probably acceptable i the interest of simplification, but when the author says, During ionization however element may lose an electron, he is misleading the student and beginner When salt ionizes, an electron is alway exchanged and it is not "lost. Again he states " when sodi m is ionized, it loses one atom from its outer orbiting shell This is not

so. It exchanges an electron not an atom. This type of loose, careless and incorrect writing is scattered throughout the book. The book is profusely illustrated with excellent reproductions of electrocardiograms and many vectorcardiograms. It is unfortunate that each lead was not always labeled directly rather than by a code at the side and top of the illustrations, as was done in many instances (see Figures 469 472 and many others) Such labeling reduces the effectiveness of otherwise well-reproduced tracings. Better labeling would be of advantage to the reader when serial tracings with complexes of different magnitudes are shown (see Figures 256 and 257 for example) The discussions of the electrocardiographic abnormalities in some disease states are not adequate. For example on page 583 the author says that there is slow bradycardia in hypothyroidism and there may be ST segment and T wave changes," but he fails to say what they are. He attributes the increased QRS amplitude in hyperthyroidism to increased stroke volume (page 583).

This is not a good book. There are some very good illustrations, but the book offers little, if anything to recommend it even to students or to beginners.

Resuscitation and Cardiac Pacing. Edited by Gavin Shaw B.Sc., George Smith M D and Thomas J Thomson M B., Philadelphia 1965 F.A. Davis Company 256 pages Price $6.

This is the proceedings of a conference on the subject held in Glasgow during March, 1964 The discussions include pathology of the arrested circulation, causative factors in circulatory arrest management of arrest arrhythmias and heart block and cardiac pacing. Aspects of biochemical disturbances the apparatus electrodes after-care, and drowning are among the many problems considered by the group. The book is a concise, brief presentation. It should be of interest to all cardiologists, anesthetists, and surgeons. It is recommended to those who wish to learn how to resuscitate a patient with circulatory arrest. The bibliographies are good. Unfortunately if there were any discussions after the presentation of each paper at the symposium these discussions were not included. This is a good book.

Shock and Hypotension. The Twelfth Hahnemann Symposium. Edited by Lewis C. Mills, M D and John H Moyer M D New York, 1965 Grune & Stratton Inc. 718 pages. Price $29

This is the proceedings of the Twelfth Hahnemann Symposium There is really little new presented. The book should provide very little to the knowledge of the experts in the field but could assist those who are interested in learning something about shock and hypotension. The book is well illustrated and the bibliography after each paper is good. As with all symposia, the contributors essentially summarize work which they have already published elsewhere. Nevertheless this book provides a good review of aspects of the work of investigations of shock.

Myokardose Myokarditis Morphologie und Pathogenese. By Gerd Gabler Jena 1965 Gustav Fischer Verlag 215 pages.

This book on myocarditis is a good presentation of this important cardiac problem. It is particularly timely in view of the present interest in the cardiomyopathies. The author has included many good histologic and electron microscopic illustrations of the lesions. The bibliography is rather extensive and includes a large number of German and other European papers which can be useful to any one interested in a more detailed study of myocarditis. This book should prove to be of particular value to those studying the cardiomyopathies as well as to cardiologists, pathologists, and internists.

Diuretic Therapy By Arthur C DeGraff M D and Alan F Lyon M D St Louis, 1965 The C V Mosby Company 41 pages. Price $3.50

There appears in each issue of the American Heart Journal a succinct practical clinical discussion of a therapeutic procedure or drug used in cardiology The section is under the guidance of Dr DeGraff and Dr Lyon This excellent publication *Diuretic Therapy* is a paperback reprint of the series of articles on diuretic therapy which appeared in the American Heart Journal. This highly practical clinical presentation should be of interest to all physicians, especially general practitioners, internists and cardiologists.

Books received

Neurological Surgery of Trauma. Prepared and published under the direction of Lt. Gen. Leonard D Heaton, Surgeon General, U S. Army Edited by Col. John Boyd Coates Jr., MC, USA and Arnold M Meirowsky M D Washington, D C., 1965 Office of the Surgeon General, 604 pages. Price $6.25.

Handbook of Physical Medicine and Rehabilitation. Edited by Frank H. Krusen M D., Frederic J Kottke M D., and Paul M Ellwood Jr., M D., Philadelphia, 1965 W B. Saunders Co., 725 pages. Price $16.50.

Need I Ever Retire? By William Evans, M.D London, 1965 Chest and Heart Association, 21 pages. Price $1.25

Nutritional Aspects of Cardiovascular Diseases. By Ezra Bajusz, M D., Ph D Philadelphia 1965 J B Lippincott Co 244 pages. Price $12

American Heart Journal

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Editorial

Paired pulse stimulation of the heart

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In the fall of 1963 Lopez, Edelist and Katz[1] pointed out that if the heart were to be driven electrically in such a way that every regular beat were followed by an early premature beat, the early premature beat would be essentially mechanically ineffective. Under such conditions, they suggested, the electrical rate of the heart would be twice as great as the rate of effective mechanical contractions. The presence of two complete cycles of electrical activity for each cycle of mechanical activity might, they reasoned, suppress ectopic beats and control tachycardias. This line of investigation was pursued by Katz and his co-workers and by Chardack and his co-workers, and later by Braunwald and his co-workers. It was also pointed out by Hoffman, Cranefield and their co-workers that this form of artificially induced arrhythmia would of necessity induce the enhancement of force of contraction known as postextrasystolic potentiation and they showed that such maintained postextrasystolic potentiation can reverse all of the features of acute heart failure in dogs.

During the past 18 months extensive investigations of many aspects of this phenomenon have been carried out on animals and on patients. A conference was held on the subject in January, 1965, and the 22 papers delivered have appeared in the May and June, 1965, issues of the *Bulletin of the New York Academy of Medicine*. It is possible, therefore, to offer a summary of the present status of this method.

Technically, it is fairly simple to induce the desired alteration in cardiac rhythm. Any of the types of electrodes used for ordinary electrical pacemaking of the heart may be employed. Special stimulators for delivering pairs of stimuli have been made available commercially, and with suitable precautions various standard physiologic stimulators may be used.

There are many precautions which must be observed with respect to isolation of the stimulators, with respect to juxtaposition of the electrodes to the myocardium, and with respect to the strength and duration of the stimulus. These precautions are discussed at length in the

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proceedings of the conference referred to above.

Several cases are now known in which the use of paired pulse stimulations has successfully controlled tachycardias which had proved to be resistant both to drug therapy and to countershock. In one such case a ventricular tachycardia with a downhill course was controlled (the electrical rate remaining high but the effective mechanical rate being half that of the electrical rate). In that case, paired pulse stimulation was discontinued after 2 days and the tachycardia had subsided. In another case paired pulse stimulation was employed for 30 days to reduce the effective mechanical rate in a seriously ill patient who eventually died. In spite of the eventual death of the patient paired pulse stimulation was the only means which succeeded in slowing an extremely ominous tachycardia. Life-threatening tachycardias which are wholly resistant to drug therapy and countershock are rare but may be regarded as suitable for treatment by paired pulse stimulation provided that it is used with the requisite skill and understanding.

Paired pulse stimulation by producing maintained postextrasystolic potentiation can greatly enhance the force of contraction of the ventricular myocardium in states of acute cardiac failure. Severe acute heart failure caused (in animals) by outflow constriction, by beta adrenergic blockade, or by difficult and delayed defibrillation is decisively improved by paired pulse stimulation during a period in which death from cardiac failure would otherwise have ensued. Such animals returned to normal cardiac function after cessation of paired pulse stimulation in experiments in which the cause of the acute heart failure was removed.

Clinical experience with the inotropic effects of paired pulse stimulators is far more limited at present. In a single case, paired pulse stimulation has been applied continuously for 13 days in a patient with chronic heart failure in an effort to bring the patient to a level of function sufficient to permit replacement of a valve. The objective signs of improvement in this case were slender and the patient did not improve enough to permit operation. The patient did show marked subjective improvement and there were no serious complications secondary to the use of the technique. No other cases in which the technique was employed to relieve heart failure have been reported.

Among the problems and hazards associated with this method are the danger of evoking arrhythmias (in particular ventricular fibrillation) and the problem of whether the technique causes an increase in the oxygen demands of the myocardium. It was clear that the technique *can* be used in both animals and human beings without evoking dangerous arrhythmias; it is also clear that faulty use of the technique or its use in certain not yet fully defined clinical states may result in such arrhythmias. No agreement has been reached on the problem of the effect of paired pulse stimulation on the oxygen demands of the myocardium. Certain evidence suggests that there is a significant increase. Other evidence suggests that a concomitant increase in coronary artery flow may compensate for any increased needs for oxygen. It has also been suggested that the increased efficiency of contraction may actually lessen the needs for oxygen.

It is universally agreed that the technique and the wide variety of effects which it produces in the heart raise a host of questions of great importance to cardiac physiology and clinical cardiology. These questions are under investigation in many clinics and laboratories. It is also agreed that the enhancement of the force of contraction and the antiarrhythmic effect of paired pulse stimulation deserve careful but cautious clinical investigation. It is thought that the technique should be used at present, only by persons familiar with the underlying physiologic principles, preferably chiefly by persons who have thoroughly familiarized themselves with its effects by studying it on animals, and chiefly in clinical situations of an unquestionably life threatening nature that have failed to respond to conventional therapy. The technique is most emphatically in an investigative state; many questions as to its safety and value must be answered. Nevertheless it is possible that it will have genuine clinical value and it has already

provoked many important experiments and a re-examination of many aspects of cardiac physiology

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Clinical communications

The effect of upright posture on right ventricular volumes in patients with and without heart failure

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A change in posture from the supine to the upright position in normal man produces significant circulatory changes. Since the introduction of cardiac catheterization and the direct Fick and dye-dilution methods of determining cardiac output, many investigators[1-9] have shown that minute output falls as a result of a fall in stroke output. Roentgenographic studies suggest further that such changes in posture result in a decrease in over-all heart size.[1-3] Information in regard to the effects of similar postural shifts on circulatory changes in patients with congestive heart failure is fragmentary.[12-14]

The development of techniques for measuring ventricular volume led us to study quantitatively the changes in stroke volume, right ventricular end-diastolic and end-systolic volumes, cardiac output, and heart rate that occur when a supine subject is tilted to the upright position. The studies were carried out on subjects without and with heart failure.

Methods

The study group consisted of 8 subjects without heart disease and 8 patients with congestive heart failure. The patients who had no known cardiovascular disease either were recuperating from a minor surgical procedure or had recovered from a medical disorder. The 8 patients with congestive heart failure had the usual classic findings. Although all were being treated with digitalis at the time of the study, they still had dependent edema. In all of the patients except one (No. 8) the left ventricle was primarily involved and the congestive heart failure was thought to be secondary to initial left ventricular decompensation. Only subjects with normal sinus rhythm were studied.

Cardiac catheterization was performed without the use of sedatives and after the subjects had eaten a light breakfast. A No. 8 double-lumen cardiac catheter was inserted into the main pulmonary artery. The catheter was positioned so that the

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proximal lumen lay in the right ventricle close to the tricuspid valve, and the distal end sealed with a fast responding thermistor bead lay in the pulmonary artery. Details of the method, including its limitations, have been reported elsewhere.[14-17]

Multiple recordings of pulmonary arterial thermodilution curves were made in rapid succession, first while the subject was resting in a supine position and then after he had been tilted upright. Each thermodilution curve was recorded after approximately 3 or 4 ml. of chilled saline had been injected into the right ventricle. Injections were made with a compressed air-driven syringe. The syringe is actuated by an electrocardiographic signal and contains a variable electronic delay circuit that permits injections to be accomplished in one diastole. The mean of all of the multiple thermodilution recordings in any subject was used as the value for that subject. A 3-minute collection of expired air for the determination of oxygen consumption was made during the thermodilution recordings. As soon as the last recording was made, samples of arterial and mixed venous blood were drawn for calculation of cardiac output by the direct Fick method.

After completion of the resting supine studies, the subject was tilted to an upright position of 60 degrees. Thermodilution recordings and determinations of cardiac output were then repeated after the subject had rested quietly in the upright tilt position for 5 minutes. All subjects were instructed to avoid contracting their leg muscles and to rest as inertly as possible on the fluoroscope table.

Absolute values of ventricular volumes were obtained by combining the thermodilution technique with the direct Fick method. Stroke volume (SV) was calculated from the direct Fick cardiac output data and the pulse rate. The ratio of right ventricular end-systolic volume (ESV) to end-diastolic volume (EDV), or the fraction of the diastolic volume remaining after contraction ceases, was measured from pulmonary arterial thermodilution curves registered after the rapid injection of cold saline into the right ventricle. The calibration of thermistor resistance against temperature is essentially linear over the small range of temperature involved in these studies. Consequently, the ESV/EDV ratio was obtained directly from each curve by averaging the ratios D-3/D-2, D-4/D-3, D-5/D-4, and so on, where D represents the distance from the base line to the end-diastolic exponential washout plateau for that beat. On occasion in the patients with congestive heart failure, the washout curve decayed so gradually that a series of distinct downstroke steps could not be seen. In these cases the downstroke was assumed to be an exponential and the following formula was applied:

$$ESV/EDV = \left(\frac{Y_n}{Y_o}\right)^{\frac{1}{n}}$$

where Y_o = distance from the base line of the point near the onset of the exponential downstroke and Y_n = the distance from the base line of a comparable point in the cardiac cycle n beats later.

Absolute ESV and EDV were then obtained by the following formula:

$$EDV = \frac{VS}{1 - ESV/EDV}$$

$$ESV = EDV - SV$$

Results

The values for SV, ESV, EDV, ESV/EDV, and heart rate for the subjects without heart disease while resting supine and after being tilted to a 60-degree upright position are summarized in Table I. Table II summarizes similar observations on the subjects with congestive heart failure. Table III summarizes the average changes resulting from being tilted upright to 60 degrees in the two groups of subjects.

Tilting to the upright position in the subjects without heart disease produced an average fall of 31.4 per cent in stroke volume and an average decrease of 16.7 per cent in end-diastolic volume (Fig. 1). Tilting also resulted in an increase of 14.9 per cent in the residual fraction or ESV/EDV ratio, whereas the heart rate increased by an average of 14.8 per cent (Fig. 2).

In contrast, in the patients with congestive heart failure, upright tilting produced no significant changes in heart rate, stroke volume, end-systolic volume, end

Table I Effect of posture on right ventricular volume and pressures in subjects without heart

Subject No	*Age (yr)*	*BSA (M^2)*	*Position*	*Right ventricular pressure (mm Hg)*
1	46	1 74	Recumbent	16/1
			60° tilt	
2.	40	1 88	Recumbent	24/5
			60° tilt	
3	45	1 80	Recumbent	17/1
			60° tilt	
4.	43	1 52	Recumbent	22/4
			60° tilt	
5.	56	1 64	Recumbent	28/4
			60° tilt	
6.	56	1 87	Recumbent	22/3
			60° tilt	
7	43	1 82	Recumbent	22/5
			60° tilt	
8.	38	1 55	Recumbent	20/4
			60° tilt	

Mean (Recumbent) ± S.D

SV Stroke volume *ESV* End-systolic volume *EDV* End-diastolic volume.

Table II Effect of posture on right ventricular volume and pressures in patients with congestive

Subject No.	*Age (yr)*	*BSA (M^2)*	*Diagnosis*	*Position*	*Right ventricular pressure (mm. Hg)*
1	50	1 88	PMD	Recumbency	74/19
				60 tilt	
2.	63	2 25	ASHD	Recumbency	41/12
				60° tilt	
3	42	1 78	HCVD	Recumbency	34/4
				60° tilt	
4	58	1 74	HCVD	Recumbency	52/3
				60° tilt	
5	45	1 84	HCVD	Recumbency	39/7
				60° tilt	
6.	63	1 61	ASHD	Recumbency	48/10
				60° tilt	
7	59	1 64	ASHD	Recumbency	37/10
				60° tilt	
8.	51	1 48	PHD	Recumbency	61/14
				60° tilt	

Mean (Recumbency) ± S.D

PMD: Primary myocardial disease *ASHD*: Arteriosclerotic heart disease *HCVD*: Hypertensive cardiovascular disease *PHD*: Pul

*disease**

ESV/EDV (%)	*Rate* (beats/min.)	*SV* (ml./M^2)	*ESV* (ml./M^2)	*EDV* (ml./M^2)	*O consumption* (ml./min.)
59 4	101	30	45	75	253
71 1	121	20	50	70	273
60 3	112	35	53	88	192
67 9	116	18	37	55	196
57 2	78	32	42	74	208
60 0	86	23	34	57	223
62 9	100	36	60	96	209
71 9	100	31	79	110	209
59 3	96	55	80	135	226
64 1	102	37	67	104	219
47 1	70	50	45	95	272
61.5	81	35	56	91	281
51 5	67	43	47	90	244
63 7	106	21	37	58	331
60 7	88	52	80	132	228
63 2	92	41	69	110	246
57 3 ± 5 3	89 ± 16	41 6 ± 9 7		98 1 ± 23 3	

*heart failure**

ESV/EDV (%)	*Rate* (beats/min.)	*SV* (ml./M^2)	*ESV* (ml./M^2)	*EDV* (ml./M^2)	*O consumption* (ml./min.)
70 6	98	28	68	96	272
64 0	96	28	49	77	284
57 9	85	38	57	95	345
69 8	87	28	70	98	368
67 7	71	38	81	119	249
71 7	79	34	85	119	271
80 1	82	25	99	124	189
83 4	87	22	110	132	210
66 3	83	29	58	87	253
64 2	93	32	58	90	326
56 0	73	29	36	65	223
63 7	70	32	57	89	265
58 8	73	31	46	77	200
62 9	80	28	48	76	256
89 4	76	23	194	217	178
89 8	77	23	202	225	198
68 4 ± 12 0	80 ± 9	30 1 ± 5 5		106 5 ± 49 7	

...monary heart disease (cor pulmonale) *SV* Stroke volume *ESV* End-systolic volume *EDV* End-diastolic volume.

Table III *Average change from supine*

	Normal	Congestive heart failure
Rate (beats/min.)	+11 5 (p < 05)	+3 5 (p > 05)
Stroke volume (ml./M²)	−13 3 (p < 01)	−1 8 (p > 2)
End-diastolic volume (mL/M²)	−16 3 (p < 05)	+3 4 (p > 5)
Residual fraction (%)	+8 1 (p < 01)	+2 9 (p > 2)

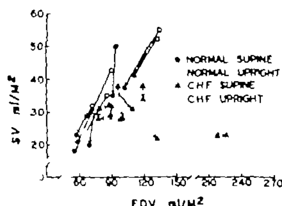


Fig. 1 Tilting to the 60-degree upright position produced a large drop in stroke output and a lesser drop in right ventricular EDV in subjects without heart disease. No consistent changes were observed after tilting in patients with congestive heart failure

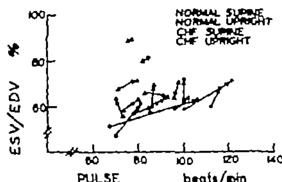


Fig. 2 Tilting to the 60-degree upright position produced an increase in pulse rate and right ventricular ESV to EDV ratio in subjects without heart disease. Similar tilting in patients with congestive heart failure produced no comparable changes.

diastolic volume or residual fraction (Figs. 1 and 2)

Discussion

Subjects without heart disease The effect of the upright position on cardiac output in normal subjects has been the subject of intensive investigation for many years. Prior to the development of methods of cardiac catheterization in man the results of such studies were somewhat contradictory.[15-21] Since cardiac catheterization has been used a number of investigators have demonstrated that assumption of the upright position results in a pronounced fall in stroke output.[1,2] Our studies confirm that a large drop in stroke output and a somewhat less pronounced decrease in cardiac output take place when a normal subject is tilted from the supine to the upright position (Fig 1) The values for right ventricular EDV and the residual fraction or ESV/EDV in these subjects were comparable to those reported by us in a previous study of volumes in recumbency in a similar group of subjects without heart disease.[14] Tilting the fluoroscope table on which the patient was lying quietly to a 60-degree upright position resulted consistently in a significant fall in right ventricular EDV (Fig 1) This finding confirms that the right ventricle participates in the generalized reduction in cardiac size observed roentgenographically.[10,11] Since the fall in stroke output was greater than the fall in right ventricular EDV the right ventricular residual fraction or ESV/EDV ratio increased with tilting into the upright position (Fig 2) This finding coincides with our previous observation that the ventricular residual fraction tends to increase as the EDV decreases in a variety of circumstances[22,23] and does not necessarily imply any decrease in myocardial performance

We interpret these results as indicating that tilting a subject to an upright position while contraction of leg and abdominal muscles is kept at a minimum results in a gravitational pooling of blood within the distensible venous tree which is only

partly compensated for by postural reflexes. Since the resultant increase in venomotor tone is insufficient to compensate for the increased hydrostatic pressure venous return decreases. With the fall in venous return and the resultant decrease in the diastolic size of the heart stroke volume falls in accordance with the Starling mechanism This decrease activates arterial pressor receptors, leading to reflex sympathetic stimulation and a resultant increase in heart rate, which compensates in part but not completely for the fall in stroke volume.

Patients with congestive heart failure The effect of upright tilting on stroke volume in patients with congestive heart failure has not been thoroughly studied Although such studies have been carried out in patients with various types of heart disease,[21,22] we were able to find only two previous references to the effects of upright tilt on stroke volumes specifically in patients with congestive heart failure. Taquini, Fermoso, and Aramendia[13] noted that over half of their series of patients who were studied during heart failure failed to show the usual fall in stroke output when they were tilted to the upright position. Similar results were obtained by Eliasch Lagerlöf and Werkö[23] in 2 patients with mitral stenosis who were in congestive heart failure. Our results have consistently demonstrated that upright tilting does not result in a fall in SV in patients with congestive heart failure, in contrast to subjects without heart disease (Fig 1) Sharpey-Schafer[24] came to a similar conclusion in regard to patients with heart failure on the basis of the observation that intra-arterial blood pressure does not change with tilting

Our observations indicate that the upright posture also does not result in a decrease in right ventricular end-diastolic volume in subjects with congestive heart failure (Fig 1) Since neither stroke volume nor end-diastolic volume change no change occurs in the residual fraction or the ESV/EDV ratio (Fig 2) We attribute the lack of change to resistance to the gravitational pooling of blood in the venous tree resulting from underlying abnormalities of the peripheral circulation in the patient with heart failure. These abnormalities consist first, of an increase in plasma volume as a result of the retention of salt and water Secondly the edema results in an increase in tissue pressure, which tends to decrease venous distensibility Thirdly venomotor tone may be increased as well[26] The net effect of these factors is to raise venous pressure and to minimize any shift of blood volume from the central circulation into the peripheral circulation when the patient is tilted upright. Consequently the upright posture produces no detectable change in end-diastolic volume of the right ventricle of the failed heart. The stroke volume which is initially low remains low Only a minimal change in heart rate occurs and consequently cardiac output does not change. The use of venous congestion cuffs, which tend to cause peripheral venous pooling and decreased venous return also produce little change in cardiac output in patients with congestive heart failure, but do cause a significant fall in normal subjects.[27]

The finding that the end-diastolic volumes during recumbency in patients with congestive heart failure frequently do not differ from those in subjects without heart disease confirms our previous observations in a different group of subjects.[10] At that time, we could not reconcile the differences in heart size by roentgenography in normal subjects and patients with heart failure and our inability to demonstrate any differences in right ventricular volume in the two groups. Although we presented a number of possible explanations, the results of the present study suggest a further explanation of this paradox. Although the volumes in the two groups are comparable during recumbency they are not comparable when the subjects are upright since upright tilting results in a distinct fall in right ventricular end-diastolic volumes only in patients without heart failure Consequently in the upright position (the position in which the patient is generally placed for chest x ray examination) right ventricular volumes are greater in subjects with heart failure than in those without heart disease.

Summary

The effects of posture on stroke volume right ventricular end-diastolic and end systolic volumes, cardiac output, and heart rate were studied in subjects witho

disease and patients with congestive heart failure. Cardiac catheterization was performed and right ventricular volumes were measured by combining a direct Fick cardiac output determination with a thermodilution technique, while the subjects were supine and after they had been tilted to a 60-degree upright position. In the normal subjects, upright tilting resulted in a profound fall in stroke volume, an increase in heart rate, and a significant decrease in the size of the right ventricle although the residual fraction increased. In contrast, in subjects with congestive heart failure, tilting to the upright position caused no significant changes.

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Cardiorenal hemodynamic effects of ethacrynic acid

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Ethacrynic acid is a potent oral diuretic and saluretic agent with the structural formula of 2,3-dichloro-4-(2 methylene-butyryl) phenoxyacetic acid.[1] It has no nitrogen or sulfonyl groups, does not inhibit carbonic anhydrase, and is active in the presence of systemic acidosis and alkalosis. Diuresis increases when ethacrynic acid is given with chlorothiazide or a mercurial.

Reports by Goldberg and associates,[2] later confirmed by MacGaffey and associates,[4] point to a novel site of action for ethacrynic acid. It reduces the clearance of free water during water diuresis and decreases reabsorption of solute free water during hydropenia, suggesting interference with the reabsorption of sodium in the ascending loop of Henle and reduction of the concentration of sodium in the medullary portions of the kidney. The magnitude of the sodium diuresis suggests further the possibility of rejection of sodium or chloride in the proximal convoluted tubule of the kidney.

Our study was designed to compare the effects of ethacrynic acid on systemic hemodynamics, renal function, and electrolyte excretion in patients with a variety of clinical disorders and in normal persons, so that we might better understand the action of the drug and define its clinical usefulness.

Materials and methods

Patients. We drew all of our patients from the wards of the University Hospitals, Iowa City. We made simultaneous measurements of the acute effects of ethacrynic acid (45 to 90 mg. given intravenously) on the cardiac hemodynamics and renal function of 6 hypertensive patients

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and 3 normotensive subjects. Four men and 2 women comprised the hypertensive group, ranging in age from 30 to 51 years (mean age, 41.3 years). The normotensive group was comprised of 2 women and 1 man, ranging in age from 23 to 43 years (mean age, 34 years). We made similar measurements in a third group comprised of 5 hypertensive patients who ranged in age from 23 to 62 years (mean age, 45 years) after intravenous administration of an equivalent volume of isotonic saline solution. In 3 other persons, 1 hypertensive patient and 2 normotensive subjects, only measurements of renal function and electrolyte excretion before and after ethacrynic acid were made.

Six hypertensive patients and 3 normotensive subjects were studied before and after 4 to 7 days of oral ethacrynic acid, 1.5 mg. per kilogram per day. The hypertensive patients who served as control subjects during the acute studies received an ethacrynic-acid placebo twice a day for 3 days and then were re-examined.

Renal function was measured before and after intravenous ethacrynic acid (12.5 to 25 mg.) in 1 patient with diabetes insipidus, in 3 with edema from cirrhosis of the liver, and in 2 with edema due to congestive heart failure.

Plan of investigation. Measurements were made with the subject in the supine position and in a fasting state. No sedative was given. The patient drank a liter of water 1 hour before the study, and a Foley catheter was placed in the bladder for the collection of urine. After priming doses of sodium para-aminohippurate (PAH) and inulin, an infusion pump maintained a constant infusion of a solution containing 1 per cent PAH and 4 per cent inulin. A small catheter was introduced through the basilic vein and advanced until its tip was lying free within the right atrium. A Cournand needle was placed in a brachial artery. After a 45- to 60-minute period of equilibration, urine was collected by means of air washout during 3 accurately timed 15-minute periods. Samples of arterial blood were drawn in the middle of each period. Immediately after initial control studies of renal function, triplicate measurements of heart rate, mean right atrial and systemic mean arterial pressures, and cardiac output were made. Measurements of renal function and cardiac hemodynamics were made at 30, 60, and 90 minutes after intravenous infusion of ethacrynic acid via the right atrial catheter over a period of 3 to 10 minutes. The ethacrynic acid was diluted with isotonic saline solution to a concentration of 10 mg. per milliliter. The control hypertensive patients received an equivalent volume of isotonic saline solution.

In addition to the renal and hemodynamic studies, the following measurements were made in all patients in the subacute phase of the study before and on the last day of treatment with oral ethacrynic acid: body weight, blood volume, serum electrolytes, urea nitrogen and creatinine, uric acid, glutamic-oxaloacetic transaminase, bilirubin, blood sugar, hematocrit, white blood count, platelet count, urinary protein and glucose.

Methods

RENAL STUDIES. The samples of blood and urine were analyzed for inulin,[6] PAH,[6] Na,[7] K,[7] Cl,[8] uric acid,[9] and osmolality by freezing point depression. Urine for pH was collected under oil, and the determination was made with a Beckman model GS pH meter. Clearance of inulin (C_{IN}) was used as a measure of glomerular filtration rate, and that of para-aminohippurate (C_{PAH}) for estimated renal plasma flow. Filtration fraction (FF) and clearance of uric acid (C_{UA}) and of osmoles (C_{OSM}) were also estimated. Clearance of free water (C_{H_2O}) and tubular rejection ratios for sodium (excreted/filtered × 100), potassium, chloride, and uric acid were calculated. All values were corrected to a body surface area of 1.73 square meters.

CARDIAC STUDIES. Statham strain gauges recorded pressures from the right atrium and brachial artery, and electrical integration provided mean pressures. Recordings of pressure were made immediately before determinations of cardiac output.

The catheter in the right atrium was filled with indocyanine green dye and connected through a 3-way stopcock to a dye reservoir and injection system. The needle in the brachial artery was connected through a short, small bore polyethylene tube to the cuvette of a Gilford densitometer. One milliliter of blood was added to

each ampule of dye in order to avoid errors in calibration by absorption of dye on tubing or glassware. Approximately 2.8 mg. of dye was used for each injection into the right atrium; dye curves were obtained by drawing arterial blood through the densitometer with a constant-speed pump at a rate of 30 ml. per minute. Three-point calibration curves were made in each study. Cardiac output was calculated by the Stewart-Hamilton method. Total peripheral resistance was calculated in terms of dynes sec. cm $^{-5}$. Lead II of an electrocardiogram measured heart rate during each determination of cardiac output. Dye curves, heart rate, and blood pressures were recorded with a Sanborn direct writing oscillograph.

BLOOD VOLUME. Total blood volume was measured with I^{131}-labeled albumin in a Volemetron, according to the method of Williams and Fine[10] as modified by Buckwalter and associates.[11] Blood from the right atrium served for estimating packed cell volume.

STATISTICAL ANALYSIS. Student's t test for paired data was used for statistical analysis of the data before and after infusion within each group at each measured time interval. In addition statistical comparisons (t tests) were made between the hypertensive patients given ethacrynic acid and those getting isotonic saline solution in the acute study, and between those on ethacrynic acid and those receiving placebo in the subacute study.

Results

Acute studies. Analyses of initial control values showed no statistically significant differences (at the 5 per cent level) in regard to age, body surface area, supine mean arterial pressure, heart rate, mean right atrial pressure, cardiac index, or calculated total systemic resistance between the hypertensive patients given ethacrynic acid and those given isotonic saline solution. There was also no significant difference in control values of glomerular filtration rate, estimated renal plasma flow, filtration fraction, clearance of uric acid, urine volume, or urine pH between the hypertensive patients who received ethacrynic acid and those treated with placebos, nor was there any difference in the pre-drug tubular rejection ratios for sodium, potassium, chloride, or uric acid between these groups.

RENAL FUNCTION STUDIES (TABLES I AND II). After intravenous ethacrynic acid glomerular filtration rate fell significantly during the third collection period in patients with edema and with hypertension; it fell in normotensive subjects in both the second and third periods. No change in this value followed intra-atrial saline in the control hypertensive group. Estimated renal plasma flow did not change significantly in any group. Filtration fraction fell slightly 60 minutes after ethacrynic acid in normal subjects and 90 minutes after the drug in patients with hypertension, reflecting the significant concurrent reduction in glomerular filtration rate in these groups.

EFFECT OF INTRAVENOUS ETHACRYNIC ACID ON URINE ELECTROLYTE EXCRETION, VOLUME, AND PH (TABLES I AND II). The flow of urine increased within minutes after the intra-atrial administration of ethacrynic acid. Volume increased significantly at 30 and 60 minutes in patients with hypertension and at 30 minutes in subjects with normal blood pressure. A more sustained diuretic effect was noted in the patients with edema (Table II), in whom the volume of urine increased significantly in all three periods after ethacrynic acid. In contrast, the volume of urine decreased significantly in the hypertensive patients who had received saline (8.2 ml./min. $\pm$ 3.1 control to 3.8 ml./min. $\pm$1.9 at 90 minutes after saline, Table I). When a comparison of the change in flow of urine from control was made between the treated and untreated subjects, it was apparent that a diuresis had actually been produced in all periods after ethacrynic acid.

Urine pH fell in the hypertensive and normal subjects who received ethacrynic acid but did not change in the saline-treated group or in the patients with edema. The tubular rejection of sodium was most marked during the first 30 minutes after the drug in hypertensives and normotensives, and was greatest at 60 minutes in patients with edema, but the increases were significant at each period in all patients receiving the drug. The

Table I. Effects of intravenous ethacrynic acid on renal function and on the excretion of electrolytes in hypertensive patients and normotensive subjects

	Pretreatment levels ± S.E.†	30 Minutes after drug ± S.E.	60 Minutes after drug ± S.E.	90 Minutes after drug ± S.E.
Hypertensive patients receiving ethacrynic acid (N =)				
Glomerular filtration rate (ml./min.)	99 ± 12	105 ± 15	91 ± 11	77 ± 7*
Renal plasma flow (ml./min.)	497 ± 73	535 ± 87	491 ± 69	443 ± 61
Filtration fraction (%)	23.0 ± 2.0	23.0 ± 2.0	22.0 ± 2.3	21.0 ± 1.8
Clearance of uric acid (ml./min.)	9.7 ± 2.5	13.1 ± 4.7	8.6 ± 2.7	5.0 ± 1.2
Sodium (% E/F)	1.3 ± 0.5	13.7 ± 2.5**	14.3 ± 2.8**	8.0 ± 1.9**
Potassium (% E/F)	19.7 ± 1.9	51.0 ± 6.1***	59.0 ± 7.4**	49.3 ± 7.7
Chloride (% E/F)	1.6 ± 0.4	21.0 ± 1.8**	22.7 ± 2.9**	12.6 ± 1.9**
Uric acid (% E/F)	9.7 ± 2.0	11.7 ± 2.7	8.7 ± 2.0	5.9 ± 1.8**
Urine volume (ml./min.)	6.6 ± 1.4	19.2 ± 2.9*	17.5 ± 2.8**	8.3 ± 1.4
Urine pH	6.22 ± 0.14	6.12 ± 0.20	5.68 ± 0.28	5.35 ± 0.25
Normotensive subjects receiving ethacrynic acid (N = 5)				
Glomerular filtration rate (ml./min.)	117 ± 10	106 ± 11	87 ± 8*	92 ± 15
Renal plasma flow (ml./min.)	533 ± 41	661 ± 146	454 ± 52	424 ± 78
Filtration fraction (%)	22.4 ± 1.6	17.6 ± 1.6	19.4 ± 1.0*	22.6 ± 1.0
Clearance of uric acid (ml./min.)	12.8 ± 2.1	10.7 ± 2.9	5.8 ± 1.3	3.9 ± 0.7
Sodium (% E/F)	1.2 ± 0.4	15.0 ± 2.5**	10.0 ± 2.0*	5.0 ± 0.9*
Potassium (% E/F)	16.0 ± 3.3	46.0 ± 5.8**	43.0 ± 3.6**	39.0 ± 6.1**
Chloride (% E/F)	1.0 ± 0.7	21.0 ± 2.1	15.0 ± 3.4	7.0 ± 2.2
Uric acid (% E/F)	19.0 ± 4.0	14.5 ± 3.5	11.0 ± 3.6	8.0 ± 3.6
Urine volume (ml./min.)	7.8 ± 0.58	21.5 ± 2.0*	11.0 ± 0.60	7.2 ± 1.3
Urine pH	6.21 ± 0.14	5.80 ± 0.25	4.92 ± 0.18**	4.66 ± 0.09**
Hypertensive patients receiving saline (N = 5)				
Glomerular filtration rate (ml./min.)	112 ± 11	111 ± 9	112 ± 9	105 ± 9
Renal plasma flow (ml./min.)	486 ± 63	469 ± 47	439 ± 44	417 ± 53
Filtration fraction (%)	23.6 ± 1.6	24.2 ± 1.1	25.8 ± 0.7	24.2 ± 1.3
Clearance of uric acid (ml./min.)	9.5 ± 1.2	9.0 ± 1.2	9.1 ± 0.7	8.3 ± 0.5
Sodium (% E/F)	1.4 ± 0.2	1.8 ± 0.3	1.0 ± 0.3	1.2 ± 0.2
Potassium (% E/F)	14.8 ± 2.8	16.2 ± 2.0	14.0 ± 1.7	12.4 ± 2.3
Chloride (% E/F)	1.2 ± 0.7	1.0 ± 0.7	1.2 ± 0.5	1.6 ± 1.4
Uric acid (% E/F)	8.4 ± 0.7	8.0 ± 0.8	8.2 ± 0.9	8.0 ± 0.7
Urine volume (ml./min.)	8.2 ± 1.9	8.2 ± 1.3	6.3 ± 1.3	3.8 ± 0.9**
Urine pH	6.12 ± 0.11	6.18 ± 1.5	6.10 ± 0.14	5.74 ± 0.24

*$p < 0.05$
**$p < 0.01$
***$p < 0.001$
†Standard error of the mean.

maximum increase ranged from 11 per cent in the patients with edema to 15 per cent in the normal subjects, the highest individual rate being 19 per cent. The patients who received saline showed no change in the tubular rejection of sodium, potassium, or chloride. The ratio of potassium excreted to filtered rose significantly in all periods in all patients who received ethacrynic acid, with the largest rise from 12 to 55 per cent in the patients with edema. Likewise, the excretion of chloride increased significantly in all periods in all patients who received ethacrynic acid, and the increase was proportionately greater than that for sodium or potassium.

EFFECT OF INTRAVENOUS ETHACRYNIC ACID ON EXCRETION OF URIC ACID (TABLE I). Clearance of uric acid decreased within 90 minutes in all patients who received etha

Table II. Effects of intravenous ethacrynic acid on renal function and on the excretion of electrolytes in patients with edema

	Pretreatment levels ± S.E.	30 Minutes after drug ± S.E.	60 Minutes after drug ± S.E.	90 Minutes after drug ± S.E.
Patients with edema receiving ethacrynic acid (N = 5)				
Glomerular filtration rate (ml./min.)	106 ± 13	97 ± 9	96 ± 7	90 ± 6 0*
Renal plasma flow (ml./min.)	490 ± 110	502 ± 92	492 ± 70	460 ± 94
Filtration fraction (%)	27 6 ± 7 2	22 0 ± 3 8	21 0 ± 3 4	23 0 ± 4 3
Clearance of uric acid (ml./min.)†	6 0 ± 1 7	5 0 ± 1 5	5 5 ± 1 9	4 0 ± 1 4
Sodium (% E/F)	0	9 6 ± 2 4**	11 6 ± 1 8**	8 0 ± 1 9**
Potassium (% E/F)	12 0 ± 1 3	42 0 ± 4 0**	55 0 ± 6 1**	48 0 ± 6 8
Chloride (% E/F)	1 2 ± 0 7	13 0 ± 2 1**	18 0 ± 2 1**	12 0 ± 2 2
Uric acid (% E/F)†	7 0 ± 2 3	6 1 ± 2 3	6 1 ± 2 4	5 5 ± 2 5
Urine volume (ml./min.)	3 7 ± 1 5	11 2 ± 1 5*	14 7 ± 1 4***	9 7 ± 1 2**
Urine pH	6 06 ± 0 29	5 82 ± 0 29	5 85 ± 0 36	5 81 ± 0 33

*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.
†Three patients.

Table III Comparative effects of high and low doses of intravenous ethacrynic acid on clearance of uric acid and on urine pH and volume

	High dose* (50 to 125 mg.)	Low dose (12.5 to 25 mg.)
Clearance of uric acid (ml./min.)		
Control	11 1 ± 1 7	6 4 ± 1 4
30 min. after ethacrynic acid	13 5 ± 3 6	4 3 ± 1 0
90 min. after ethacrynic acid	4 8 ± 1 0***	2 9 ± 1 0
Urine pH		
Control	6 14 ± 0 18	5 76 ± 0.25
30 min. after ethacrynic acid	5 98 ± 0 19	5 81 ± 0 24
90 min. after ethacrynic acid	5 20 ± 0 24	5 57 ± 0 39
Urine volume (ml./min.)		
Control	6 6 ± 1 5	5 0 ± 1 8
30 min. after ethacrynic acid	21 3 ± 1 8*	10 4 ± 2 3***
90 min. after ethacrynic acid	9 0 ± 0 8	6 3 ± 1 4

*N = 10.
**N = 6.
***$p < 0.001$ (comparison with control).

crynic acid. This fall was greater than could be accounted for on the basis of concomitant reductions in glomerular filtration rates. No appreciable changes were observed in patients who received saline. An early insignificant increase in the clearance of uric acid accompanied by a profound diuresis occurred in some patients who received a high dose (50 to 125 mg.) without a concurrent increase in glomerular filtration rate (Table III). The excreted/filtered ratio for uric acid was significantly lower 90 minutes after ethacrynic acid in the hypertensive patients but did not change appreciably in the other groups. When the per cent of

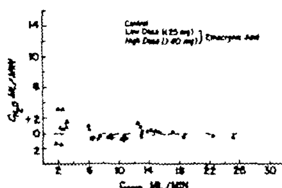


Fig 1 Relationship between the excretion of solutes and the learance of free w ter

change is calculated however the excreted/filtered ratio of uric acid decreased significantly in the normal subjects for all three collection periods It also fell in the patients with edema but the values were not significant possibly because of the small size of the group (3 patients)

FREE WATER AND OSMOTIC CLEARANCE. Fig 1 shows the clearance of free water (C_{H_2O}) the osmolar clearance (C_{OSM}) C_{OSM} rose markedly in patients who received the drug After an oral water load C_{H_2O} averaged 3 ml per minute in the control period After the diuretic it decreased sharply with the largest reduction

Table IV Acute cardiac hemodynamic effects of ethacrynic acid (I V) in hypertensive patients and normotensive subjects

	Pretreatment levels ± S.E.	30 Minutes after drug ± S.E	60 Minutes after drug ± S.E	90 Minutes after drug ± S.E
H pertensive patient given ethacrynic acid (N = 6)				
Supine mean arterial pressure (mm Hg)	145 ± 5	144 ± 6	138 ± 6	131 ± 7
Heart rate (beat /min)	84 ± 3	85 ± 4	91 ± 2	89 ± 2
C rdiac ndex (L /min /M)	3 1 ± 0 4	2 5 ± 0 3	2 4 ± 0 4†	2 3 ± 0 3†
Supine mean right atrial pressure (mm Hg)	3 1 ± 0 6	2 1 ± 0 5	1 3 ± 0 3†	1 0 ± 0 2†
Total sy temic resistance (dynes sec m)	2 380 ± 345	2 865 ± 365	2 930 ± 490	2 700 ± 480
Normotensiv subjects gi en ethacrynic acid (N = 3)				
Supine mean rterial pressure (mm Hg)	100 ± 4	87 ± 16	83 ± 8	81 ± 9
Heart rate (beat /min)	69 ± 4	73 ± 3	80 ± 5	82 ± 2
C rdiac ndex (L /min /M	2 6 ± 0 1	2 4 ± 0 2	2 2 ± 0 2	2 4 ± 0 1
Supine mean right trial pressure (mm Hg	5 0 ± 1 2	3 8 ± 0 9	4 0 ± 1 3	1 0*
Total temic resist nce (dynes sec cm)	1 610 ± 220	1 590 ± 170	1 380 ± 195	1 355 ± 245
Hypertensi patient gi en isotonic saline solution (N = 5				
Supine mean arteri l pressure (mm Hg)	135 ± 6	132 ± 3	134 ± 3	128 ± 7
Heart rate (beat /min	78 ± 6	78 ± 7	80 ± 7	79 ± 7
Cardiac index (L /min M)	2 6 ± 0 3	2 6 ± 0 4	2 6 ± 0 3	2 7 ± 0 4
Supine mean right atrial pressure (mm Hg)	4 9 ± 0 6	4 4 ± 0 4	4 2 ± 0 3	3 9 ± 0 4
Total systemic resi tance (dynes sec cm)	2 350 ± 325	2 350 ± 340	2 320 ± 280	2 280 ± 390

*p < 0 05
**p < 0 01
***p < 0 001
†Five patients
‡One patient

occurring in patients who had received the larger doses of ethacrynic acid In many instances, a negative C_{H_2O} was noted in the presence of large solute loads.

SYSTEMIC ARTERIAL PRESSURE (TABLE IV) Intragroup comparisons of the absolute levels of supine mean arterial pressure after ethacrynic acid or isotonic saline solution showed no significant differences at the 30- 60- and 90-minute periods. At the 90-minute period the average de crease in mean arterial pressure (−14 mm Hg) in the hypertensive patients given ethacrynic acid was slightly greater than the change (−7 mm Hg) in pressure in the hypertensive patients receiving isotonic saline solution ($p < 0.02$) Inter group comparisons at 30 and 60 minutes after the drug showed no appreciable differences.

HEART RATE (TABLE IV) Although the mean heart rates of the three groups tended to increase at each measured interval in no instance were they statistically different from control levels. Intergroup comparison of the two hypertensive groups showed no significant difference in heart rate at any interval.

CARDIAC INDEX (TABLE IV) Thirty minutes after ethacrynic acid the average cardiac index of the hypertensive group de creased from 3 1 to 2.5 L./min./M.² ($p < 0.05$) In only 5 of the 6 hypertensive pa tients were measurements of the cardiac output made at 60 and 90 minutes, and although the average values at these inter vals were similar to those at 30 minutes, the results were not significantly different from pretreatment levels. The average cardiac index of the normotensive subjects did not change after intravenous infusions of ethacrynic acid nor did isotonic saline solution produce appreciable differences in cardiac output. Intergroup comparison of the two hypertensive groups showed that at the 30-minute interval the reduction in cardiac output in the group given ethacry nic acid was greater than in the group given isotonic solution ($p < 0.01$)

RIGHT ATRIAL PRESSURE (TABLE IV) The mean right atrial pressures were nor mal in the three groups during the control period In the hypertensive group given ethacrynic acid mean right atrial pressure decreased significantly at 30 and 90 minutes. Except for a decrease at the 90-minute interval in the hypertensive patients given isotonic saline solution, no appreciable change in the right atrial pressures oc curred at any period in the other two groups.

TOTAL SYSTEMIC RESISTANCE (TABLE IV) Thirty minutes after ethacrynic acid the peripheral resistance of the hypertensive patients increased from 2,380 to 2 865 dynes sec. cm⁻⁵ ($p < 0.01$) Changes similar in magnitude occurred at 60 and 90 minutes but did not achieve statistical significance There were no appreciable changes in peripheral resistance in the normotensive subjects given ethacrynic acid or in the hypertensive patients after infusions of isotonic saline Intergroup comparisons of the two hypertensive groups showed a significantly greater increase in total systemic resistance at the 30-minute interval after ethacrynic acid

Subacute studies Comparison of the initial control studies of the hypertensive patients given oral ethacrynic acid with those of patients given placebo showed no significant differences in physical charac teristics or in renal or cardiac hemody namics.

RENAL STUDIES (TABLE V) The glomeru lar filtration rate fell in the patients treated with ethacrynic acid The estimated renal plasma flow increased and the filtration fraction decreased but none of these changes was significant. The clearance of uric acid fell insignificantly but when the reduction was compared to the change in the hypertensive patients given placebos, a greater fall ($p < 0.02$) was noted after ethacrynic acid Glomerular filtration rate renal plasma flow filtration fraction and clearance of uric acid did not change in the group which received placebos.

CARDIAC STUDIES (TABLE V) Systemic mean arterial pressure decreased in 5 of the 6 hypertensive patients, but in only 1 of the 3 normotensive subjects given ethacrynic acid The administration of placebo to hypertensive patients produced an average reduction in mean arterial pressure of only 2 mm Hg Although oral ethacrynic acid produced an average re duction in systemic mean arterial pressure of 15 mm Hg this depressor effect was not significantly different from the slight

Table V. Cardiac hemodynamic and renal effects of oral ethacrynic acid in hypertensive patients and normotensive subjects and effects of placebo in hypertensive patients

	Hypertensive patients given ethacrynic acid (N = 6)		*Normotensive patients given ethacrynic acid (N = 3)*		*Hypertensive patients given placebo (N = 5)*	
	Pretreatment level ± S.E.	*Treatment level* ± S.E.*	*Pretreatment level ± S.E.*	*Treatment level* ± S.E.*	*Pretreatment level ± S.E.*	*Treatment level* ± S.E.*
Glomerular filtration rate (ml./min.)	116 ± 4.2	103 ± 9.3	124 ± 15	114 ± 25	112 ± 11	113 ± 13.2
Renal plasma flow (ml./min.)	522 ± 38	540 ± 87	498 ± 43	611 ± 98	485 ± 63.3	505 ± 91
Filtration fraction (%)	23.3 ± 2.1	20.7 ± 3.5	24.7 ± 1.9	18.3 ± 1.8	23.6 ± 1.6	24.0 ± 2.7
Clearance of uric acid (ml./min.)	11.7 ± 2.9	7.5 ± 0.8	12.8 ± 2.7	9.3 ± 1.8	9.5 ± 1.1	10.0 ± 1.6
Supine mean arterial pressure (mm. Hg)	143 ± 3	128 ± 8	104 ± 8	101 ± 2	135 ± 6	133 ± 8
Heart rate (beats/min.)	80 ± 4	80 ± 2	69 ± 3	80 ± 4	78 ± 6	74 ± 6
Cardiac index (L./min./M.²)	3.2 ± 0.3	3.1 ± 0.3	2.6 ± 0.1	2.7 ± 0.2	2.6 ± 0.3	2.8 ± 0.4
Supine mean right atrial pressure (mm. Hg)	3.8 ± 0.5	4.1 ± 0.5	5.0 ± 1.2	5.2 ± 2.7	4.9 ± 0.6	4.6 ± 0.2
Total systemic resistance (dynes sec. cm.⁻⁵)	2,010 ± 210	1,990 ± 120	1,610 ± 220	1,530 ± 100	2,355 ± 325	2,290 ± 435

*None of the post-treatment values was significantly different from control values.

reduction associated with the administration of placebo ($p < 0.10$).

The heart rate of hypertensive patients did not change with ethacrynic acid or placebo; however, that of normotensive subjects receiving the diuretic increased an average of 11 beats per minute ($p < 0.10$).

There was no appreciable change in cardiac index after ethacrynic acid or the administration of placebo. Furthermore, the small average variation in cardiac output of the hypertensive group given the drug was not significantly different from that associated with placebo therapy.

The control mean right atrial pressure was normal in all three groups, and neither ethacrynic acid nor placebo produced any important change in it. Intergroup comparisons showed no appreciable differences.

Since systemic arterial pressure and flow were essentially unchanged in the three groups, post-treatment resistances were not significantly different from the control values. Likewise, a comparison of the effects of ethacrynic acid and those of placebo showed no appreciable differences.

Ethacrynic acid produced a significant reduction in body weight in hypertensive patients (Table VI). A similar loss of weight occurred in normotensive subjects given ethacrynic acid, but the small number of subjects in this group probably prevented the change from being a significant one as defined in this study. The average loss of 5 pounds by the hypertensive patients given ethacrynic acid was also greater than the average decrease of 1 pounds observed in the group given placebo ($p < 0.02$). Total blood volume fell in both groups given the drug, but the post-treatment values were not significantly different from control values. The administration of placebo did not alter blood volume. A comparison of the effects of placebo and those of ethacrynic acid

Table VI *Effects of subacute oral ethacrynic acid or placebo*

	Hypertensive patients given ethacrynic acid (N = 6)		*Normotensive subjects given ethacrynic acid (N = 3)*		*Hypertensive patients given placebo (N = 5)*	
	Pretreatment level ± S.E.	*Post-treatment level ± S.E.*	*Pretreatment level ± S.E.*	*Post-treatment level ± S.E.*	*Pretreatment level ± S.E.*	*Post-treatment level ± S.E.*
Body weight (pounds)	161 ± 17.9	156 ± 17.8	184 ± 7.6	178 ± 6.1	179 ± 18.4	177 ± 18.6
Total blood volume (liters)	5.0 ± 0.3	4.8 ± 0.3	5.2 ± 0.5	5.0 ± 0.4	5.4 ± 0.5	5.4 ± 0.4
Hematocrit	42 ± 1.2	39 ± 1.3	41 ± 2.6	39 ± 1.5	43 ± 3.1	37 ± 3.1**
Serum sodium (mEq./L.)	138 ± 2.1	137 ± 1.6	140 ± 0.8	138 ± 1.9	138 ± 0.7	137 ± 0.6
Serum potassium (mEq./L.)	4.1 ± 0.2	3.6 ± 0.1	4.1 ± 0.1	3.3 ± 0.4	4.2 ± 0.2	3.9 ± 0.2
Serum chloride (mEq./L.)	101 ± 2.2	96 ± 1.4***	105 ± 1.0	96 ± 2.1	101 ± 1.0	103 ± 1.3
Serum CO_2 content (mEq./L.)	25 ± 1.6	27 ± 1.4	22.3 ± 0.8	29.1 ± 2.0	23 ± 0.3†	23 ± 1.2†
Serum urea nitrogen (mg./100 ml.)	14 ± 1.2	19 ± 1.3	16 ± 1.7	15 ± 2.6	12 ± 2.3	11 ± 0.5
Serum creatinine (mg./100 ml.)	1.0 ± 0.1	1.1 ± 0.1	0.9 ± 0.6	1.2 ± 0.3	1.0 ± 0.1	0.9 ± 0.1
Serum uric acid (mg./100 ml.)	4.7 ± 0.3	6.9 ± 0.4***	5.3 ± 0.6	7.7 ± 0.88***	5.7 ± 1.3	5.9 ± 1.3

*$p < 0.05$.
**$p < 0.02$.
***$p < 0.01$.
†Four patients.

on blood volume in the two hypertensive groups showed no significant differences. The volume of packed cells decreased slightly in each group but the reduction in hematocrit was significant only in the hypertensive subjects given placebos.

In the hypertensive group, ethacrynic acid produced a significant reduction in serum potassium and chloride, and a significant rise in CO_2 content but serum sodium was not appreciably altered. Similar changes occurred in the normotensive subjects after ethacrynic acid but the number of subjects was small and statistically significant changes were not achieved. The administration of placebo to hypertensive patients produced only a small, but statistically significant, decrease in serum potassium.

Neither the diuretic nor placebo altered serum urea nitrogen or serum creatinine appreciably. Significant *increases in serum* uric acid were observed in both hypertensive and normotensive subjects given ethacrynic acid. In contrast, the hypertensive patients showed no such change after the placebos.

STUDIES IN A PATIENT WITH DIABETES INSIPIDUS (TABLES VII AND VIII). A comparison of the acute effects of ethacrynic acid and chlorothiazide was made in a patient with diabetes insipidus (Table VII) who initially received 500 mg. of chlorothiazide intravenously after control measurements. The volume of urine rose promptly from a control level of 8.3 ml. per minute to 14.7 ml. per minute at 30 minutes after the drug and peaked at 15.6 ml. per minute at 60 minutes. C_{osm} also rose markedly from a control of 1.1 to a peak of 7.0 ml. per minute in the second drug period. C_{H_2O} remained approximately the same or rose slightly (control 7.2 ml. per minute) to levels of 7.9, 8.5 and 7.9 ml. per minute, respectively, for the three periods.

In a second study performed 12 days later 25 mg. of ethacrynic acid was given

*Table VII. Acute effects of chlorothiazide (CTZ) and ethacrynic acid (EA) in patient with diabetes insipidus**

	Minutes	Urine volume (ml./min.) 1	2	C_{osm} (ml./min.) 1		C_{H_2O} (ml./min.) 1	2
Control periods							
1	1-30		8.5		2.8		5.7
2	31-60	9.9	9.6	1.2	2.8	8.7	6.8
3	61-90	6.8	8.6	1.0	2.7	5.8	5.9
Treatment periods		CTZ (500 mg.)	EA (25 mg.)	CTZ (500 mg.)	EA (25 mg.)	CTZ (500 mg.)	EA (25 mg.)
1	91-120	14.7	20.7	6.8	14.9	7.9	5.8
2	121-150	15.6	14.3	7.0	9.6	8.5	4.8
3	151-180	13.7	8.0	5.9	4.1	7.9	4.0

*After two 30-minute control periods, 500 mg. of chlorothiazide was given intravenously over a 5-minute period. After a 12-day interval, the second study was made. Ethacrynic acid, 25 mg., was also given intravenously over a 5-minute period, and observations were made each 30 minutes for [illegible] hours. Renal conditions were the same for both studies.

Table VIII. Effect of oral ethacrynic acid in a patient with diabetes insipidus

Day	Ethacrynic acid (mg./day)	Intake (L./day)	Urine output (L./day)	Urine (mOsm./L.)	Serum (mOsm./L.)	GFR (ml./min.)
1		9.5	10.3	194	285	144
2		11.7	13.5	143		
3	100	10.5	12.1	142		
4	100	8.8	11.6	180		
5	200	7.3	8.5	217	298	
6	200	6.5	7.6	201		
7	300*	5.9	7.3	233		
8		5.5	4.8	235	303	
9						
10						138

*[illegible], weakness, and dizziness.

intravenously after control measurements had been made. The volume of urine increased slightly more after ethacrynic acid than after chlorothiazide (control 8.9 ml. per minute; peak, 20.7 ml. per minute), but it fell to normal values more quickly. Osmolar clearance rose about the same extent (from control level of 2.8 ml. per minute to 14.9 ml. per minute) in the first drug period.

This patient also received graded doses of oral ethacrynic acid (100 to 300 mg. per day). When the dose reached 200 mg. per day, urinary volume decreased and urinary and serum osmolality increased (Table VIII). Blood pressure did not change.

Discussion

The systemic and renal hemodynamic data obtained from both the acute and subacute studies can be explained on the basis of a fall in plasma volume. The rapid diuresis of solutes and water which occurred in the acute studies, and the sustained diuresis and loss of weight in the subacute studies support this explanation. Measurements of blood volume made in the

subacute studies, although not significantly different in intragroup or intergroup comparisons tend to reflect such a fall Under these circumstances one would expect a decrease in glomerular filtration rate, reductions in blood pressure cardiac index, and right atrial pressure and an increase in heart rate and total systemic resistance. We observed all of these changes or noted trends which were statistically insignificant in some or all of the groups receiving ethacrynic acid The placebo-treated groups, on the other hand did not demonstrate significant changes or trends which would suggest contraction of blood volume The tendency for estimated renal plasma flow to increase and for filtration fraction to fall in the treated groups is not explained by contraction of plasma volume. If this were the only mechanism one would expect to see either a rise or no change in filtration fraction. The possibility that the efferent glomerular resistance was selectively reduced by the drug must be considered in this situation

Other explanations for the systemic and renal hemodynamic changes are that the drug has a direct or indirect effect on the heart and vessels of the greater circulation or that observed changes simply reflect biologic variation. Although our evidence does not completely discount these hypotheses, neither seems to us to be likely It is tempting to speculate that the alkalosis produced by ethacrynic acid was responsible for the circulatory changes by altering vascular tone and distensibility However we did not study the action of the drug in any other pH environment, and the effect of alkalosis on circulatory and renal hemodynamics is not well understood [13]

Our studies of the excretion of solutes and water after ethacrynic acid in these well-hydrated patients are consistent with the data of Goldberg and associates[3] and may be interpreted to mean that ethacrynic acid blocks the reabsorption of sodium from the ascending loop of Henle after water loading The data are also consistent with the hypothesis that the drug blocks the transport of sodium (or chloride) in the proximal tubule and has an effect on the clearance of free water in the distant portion of the nephron The increases in the excretion of hydrogen and potassium may simply reflect the increased availability of sodium to the ion exchange areas of the nephron although our data do not exclude action by the drug to cause a loss of these ions.

The excretion of uric acid after the administration of ethacrynic acid is reminiscent of that which follows chlorothiazide and acetylsalicylic acid The excretion of uric acid is influenced by factors which alter non ionic (passive) diffusion and, or interfere with active excretory and reabsorptive mechanisms. Thus the suggestive increase in the excretion of uric acid after the high dose of ethacrynic acid might result from interference with active reabsorptive mechanisms, but this is moot since we also noted an increase in flow which would tend to counter non-ionic diffusion and passively increase the excretion of uric acid Furthermore, the decrease in the pH of the urine which we noted in acute studies would normally decrease the excretion of uric acid by increasing the reabsorption of the uric acid Since these two variables are important in the excretion of uric acid and were swinging to opposite poles at the time at which the excretion of uric acid was greatest, we cannot say that ethacrynic acid was crucial to the observed uricosuria

The reduction in the excretion of uric acid at low doses and the increase in serum uric acid in the subacute studies might be explained by interference with active excretory processes, by reduction in glomerular filtration rate or by the decrease in urine pH Experiments designed to control the various factors regulating the metabolism of uric acid in man are needed to understand the significance of the changes observed in uric acid

Our clinical studies suggest, also that the contraction of plasma volume is important in renal changes, particularly the reduction in glomerular filtration rate.[12] In 3 additional patients not otherwise described here,[12] after a profound diuresis lasting from 1 to 7 days, we observed increases in blood urea nitrogen and creatinine which were readily corrected in 2 patients, we withdrew the ethacrynic acid and instituted a diet with more than 60 mEq of sodium daily in the third

we continued the drug while having the patient take a diet containing more salt.

Our observations indicate that ethacrynic acid can increase the osmolality of urine in patients with diabetes insipidus. A distinctly hypertonic urine was not elaborated but the drug increased osmolality to a greater extent than did chlorothiazide under similar conditions. This action could be explained by the rejection of sodium at the ascending loop of Henle or by a direct effect of ethacrynic acid on the tubular sites of collection. Our evidence is not sufficient to separate these alternatives.

Finally, it is apparent that the drug is an extremely powerful diuretic that has a rapid onset of action after intravenous administration and acts for at least 1½ hours. It is capable of removing large volumes of sodium and other electrolytes from the body while interfering very little with other systemic circulatory functions. We saw no adverse effect on the hemopoietic, hepatic, or central nervous-system functions. Several patients complained of mild nausea after oral and intravenous doses, the most pronounced effect being that in the patient with diabetes insipidus when a daily dose of 300 mg. was reached. In other clinical studies, ethacrynic acid frequently produced diuresis when mercurials and other diuretics were ineffective. Massive diuresis produced in edematous patients by long-term administration were attended regularly by the development of mild hypochloremic alkalosis and occasionally by azotemia, easily reversed by discontinuing the drug and administering sodium. Two seriously ill patients died after massive diuresis produced by ethacrynic acid. The diuretic potency of the drug suggests that it will have wide clinical applicability, but this same feature demands that it be used with caution.

Summary

Ethacrynic acid, studied in normal subjects as well as in patients with hypertension or edema, reduces glomerular filtration rate slightly and has little or no effect on estimated renal plasma flow while decreasing filtration fraction. It causes a prompt increase in the volume of urine with the excretion of 8 to 19 per cent of sodium filtered 30 minutes after intravenous administration. It also produces a reduction in urine pH as well as a profuse diuresis of chloride and a lesser diuresis of potassium. With large doses there is a slight increase in the excretion of uric acid, whereas with lower doses there is retention of uric acid. In well hydrated patients, the clearance of free water is reduced when osmotic clearance is maximal.

The systemic hemodynamic effects of the drug are not striking. In our study, cardiac index and right atrial pressure fell after acute administration, whereas heart rate and total systemic resistance increased slightly. Although there was a tendency for blood pressure to fall in patients treated with ethacrynic acid in both the acute and subacute studies, the post-drug values were not significantly different from control values.

The renal and systemic hemodynamic effects of the drug are best explained by a reduction in the plasma or circulating blood volume caused by the profuse diuresis of electrolytes and, to a lesser extent, water. The renal effects which we observed could be explained on the basis of a reduction in the reabsorption of sodium in the ascending loop of Henle or by an effect of ethacrynic acid on the proximal and distal tubular sodium reabsorption sites.

Ethacrynic acid increased the osmolality of the urine in one patient with diabetes insipidus slightly more than did chlorothiazide in similar studies.

Ethacrynic acid is a potent diuretic capable of causing massive loss of electrolytes and water. No adverse effects on hemopoietic, hepatic, or central nervous-system function were noted in this short-term study.

We wish to thank Mr. J. L. Ferguson for performing the measurements of blood volume and E. L. Foltz, M.D., Merck Research Laboratories, West Point, Pa., for generous supplies of ethacrynic acid and placebos.

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Aneurysmal protrusion of the posterior leaflet of the mitral valve

An auscultatory-electrocardiographic syndrome

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In previous communications from this laboratory[1-4] evidence was produced that apical late systolic murmurs are invariably due to mitral regurgitation. It was also suggested that the commonly associated mid-late systolic clicks result from abnormalities of the mitral chordae tendineae. Our conclusions were based on the results of a number of investigations, which included left ventricular cineangiocardiography and the effects on the auscultatory features of the inhalation of amyl nitrite, the injection of phenylephrine, a Valsalva maneuver, and ectopic beats. Ninety patients with either an apical late systolic murmur or a nonejection (so called mid-late) systolic click, or both, have now been studied[5] and the results have confirmed our earlier observations and postulates.

Among the 90 patients, there are 4 who presented a specific electrocardiographic pattern and in whom left ventricular cineangiocardiography showed during left ventricular systole a massive protrusion of the posterior (mural) leaflet of the mitral valve into the left atrial cavity, in addition to mild mitral regurgitation. The purpose of this paper is to describe the findings in these 4 patients, as well as in another patient in whom cineangiocardiography has not been performed.

Case reports

Case 1. A 56-year-old white woman was first seen in December, 1961. At the age of 23 she had developed a transient weakness of the left arm and was told that her heart was abnormal. After a routine examination when she was 35 years old, she had been told that a cardiac murmur was present. She remained generally well, however, until July, 1961, when she experienced a constricting pain in the central part of the chest on exercise. In November of that year a similar although more severe pain occurred at rest and was associated with sweating, breathlessness, and later with loss of consciousness for about 10 minutes. Myocardial infarction with a cerebral embolism was diagnosed. She was referred to this Cardiac Clinic for further assessment of her cardiac status.

On examination she was not in congestive cardiac failure. Her blood pressure was 180/100 mm. Hg. A left hemiparesis which also involved the left side of her face was present. The apex beat was in the fifth intercostal space and was displaced to just outside the mid-clavicular line. A quadruple rhythm was heard at the apex, and a phonocardiogram showed that the P-G interval[6] was 0.16 second. The third heart sound was remarkably late and started 0.24 second after the aortic component of the second sound (Fig. 1,a). A late systolic click and a Grade 2* late systolic murmur were also present at the apex (Fig. 1,b).

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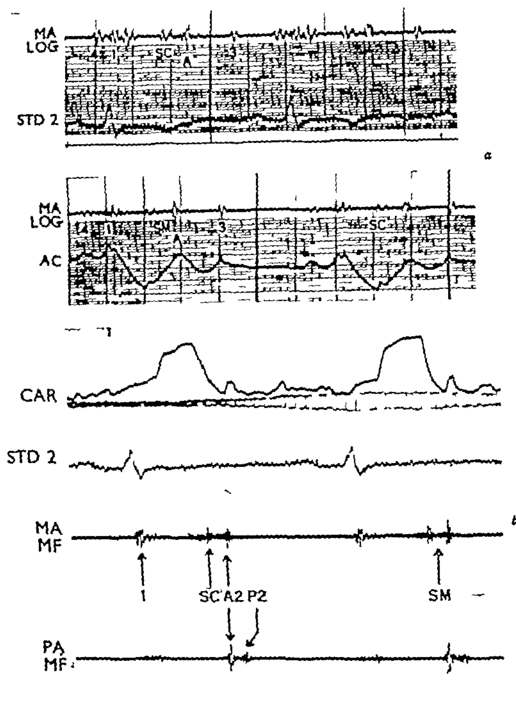


Fig. 1. Case 1. Phonocardiograms. *a*, Logarithmic tracings (Sanborn Twin-Beam Cardiette) demonstrate the quadruple rhythm and the long A-3 interval of 0.24 second. *b*, Medium-frequency phonocardiogram (New Electronic Products multichannel apparatus) showing the late systolic murmur and nonejection systolic click. Abbreviations for this and subsequent figures: *MA*, mitral area; *PA*, pulmonary area; *AC*, apex cardiogram; *MF*, medium frequency; *SM*, systolic murmur; *SC*, systolic click; *A* or *A2*, aortic component of second heart sound; *P* or *P2*, pulmonary component of second heart sound. In all tracings the distance between the heavy vertical lines equals 0.2 second.

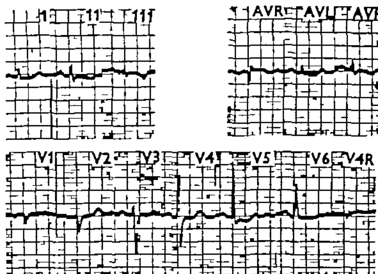


Fig. 2. Case 1. Electrocardiogram. Flattened or inverted T waves are present in Leads II, III, AVF, V_4, and V_6.



Fig. 3. Case 1. Left ventricular cineangiocardiogram in the right anterior oblique position. Massive dilatation of the posterior leaflet (*PL*) can be seen. *LA*, left atrium; *LV*, left ventricle; *Ao*, aorta.

The electrocardiogram (Fig. 2) showed inverted T waves in Leads II, III, AVF, V_4, and V_6. On fluoroscopy there was an unfolded aorta and slight left ventricular enlargement.

Six months later the patient was well and the quadruple rhythm had disappeared. The late systolic click and murmur were unchanged. Left ventricular cineangiocardiography was performed in August, 1963. Mild mitral regurgitation was demonstrated, and, in addition, the posterior leaflet of the mitral valve bulged prominently during ventricular systole (Fig. 3).

Case 2. A 48-year-old white woman seen in September, 1961, complained of intermittent palpitations, left inframammary chest pain, and breathlessness on effort of 8 years' duration. Nevertheless, she did not really regard herself as having any significant disability, and attributed her symptoms to the shock of seeing my husband taken by a crocodile. There was no history of rheumatic fever.

Examination revealed a loud late systolic click followed by a late systolic murmur of Grade 2[a] intensity (Fig. 4). The components of the second heart sound were very soft and there were no gallop sounds. Her blood pressure was 145/90 mm. Hg.

An electrocardiogram showed inverted T waves in Leads II, III, AVF, and V_4 (Fig. 5). On radioscopy there was slight enlargement of the left atrium and left ventricle.

Left ventricular cineangiocardiography was performed in November, 1961, and showed mild mitral regurgitation and massive dilatation of the posterior mitral valve leaflet.

Her subsequent attendance at the Clinic has been irregular, but when she was last seen in September, 1964, she had no cardiac symptoms. The clinical examination and electrocardiogram were unchanged, except that the T wave in Standard Lead II had become upright.

Case 3. This 6-year-old boy was seen in October, 1963, for assessment of a systolic murmur that had been heard on routine medical examination at school. He was asymptomatic and had not had rheumatic fever.

Two mid-late systolic clicks followed by a Grade 2[a] late systolic murmur were audible at the apex. The most striking feature on clinical auscultation, however, was an extremely loud clicking sound at

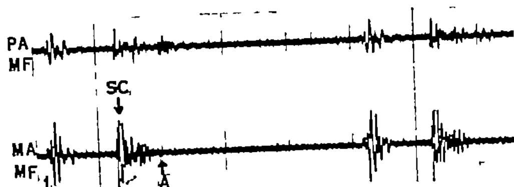


Fig. 4 Case 2. A loud late systolic click is followed by a systolic murmur

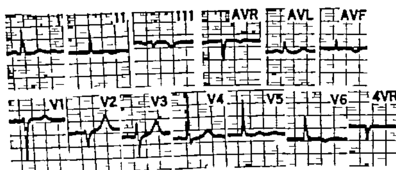


Fig. 5 Case 2. Electrocardiogram. The T waves in Leads II, III, AVF, and V_6 are inverted. Tall T waves can be seen in Leads V_2 and V_3. (From Barlow, J. Chron. Dis. 18:665, 1965, by permission of the Editor and Pergamon Press, Ltd.)

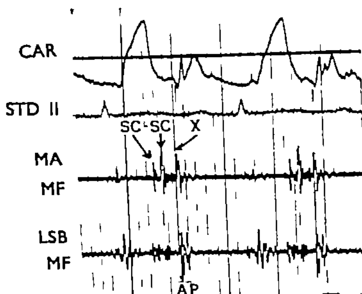


Fig. 6 Case 3. Medium-frequency phonocardiograms recorded at the apex (*MA*) and lower sternal border (*LSB*). Two systolic clicks and a late systolic murmur are clearly seen. The loud vibration (marked *X*) at the apex occurs about 0.02 second before the dicrotic notch of the carotid tracing (*CAR*) and simultaneously with the aortic component (*A*) of the second sound as recorded at the sternal border. For further discussion on this sound (X) see text.

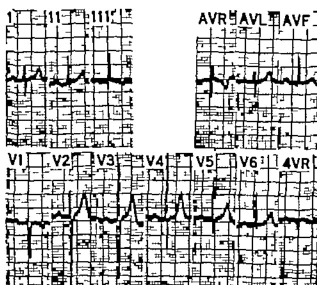


Fig. 7 Case 3 S-T segments are slightly elevated in Leads II III and AVF Small Q waves are seen in Leads III and AVF The T waves in Leads V₂, V₃, and V are tall and peaked

the end of stole which was onsiderably louder at the apex than at the base of the heart The click ing quality w suggestive of a ery late y tolic click, but phonocardiogram (Fig 6) howed that the vibration was ynchronous w th closure of the aortic v lve. In our tudy of nonejection licks n 73 patients, none ha occurred so lat in y tole and an attempt wa made therefore to sess the origin of this sound on the basis of its behavior during hemodynamic hanges caused by amyl nitrite, phenylephrine and a Valsal a maneuver. The results of these procedures, although perhaps not ompletely onclusi e suggest that the sound is, in fact, a loud aortic omponent of the second sound rather than a very lat systolic lick. Al though it became softer during the training phase of the Valsalv maneuver nd fter the i halation of amyl nitrite there was never a hange in it time relationsh p to either the dicrotic notch of the carotid tracing or the aortic component of the second heart sound recorded at the base of the heart Thi wa in contrast to the two mid-late sy tolic licks, both of which like other lick th t we ha e studied, moved earlier and became softer t this t me After the injection of phenylephrine the sound became louder and later which is gain compatible with the aortic closure sound

An electrocardiogram (Fig 7) showed a slightly elevated S-T segment in Lead II III and AVF Small Q waves were present in Leads III and AVF The T wave was inverted in Lead III No abnormalities were found on fluoroscopy but left ventricular cineangiocardiography confirmed the presence of mild mitral regurgitation and protrusion of the posterior leaflet (Fig 8) The aortic val e appeared to be normal in both the left entricular cineangiocardiogram and a retrograde aortogram and we are unable to explain why the aortic closur sound is apparently increased in intensity nd is clicking in quality

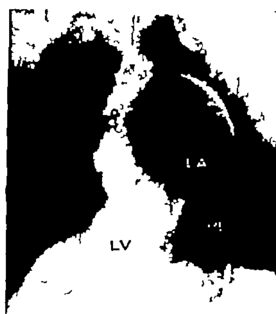


Fig 8 Case 3 Left ventricular cineangiocardiogram i the left lateral position. Protrusion of the posterior leaflet (*PL*) can be seen.

Sever l weeks fter this patient first attended the Clinic his mother informed us that she was a niece of the patient of Case 2 The possibility of a f milial factor w thus raised and an attempt was made therefore t examine all members of the family who could be traced nd who would cooper ate A s shown in Fig 9 17 relatives of these two

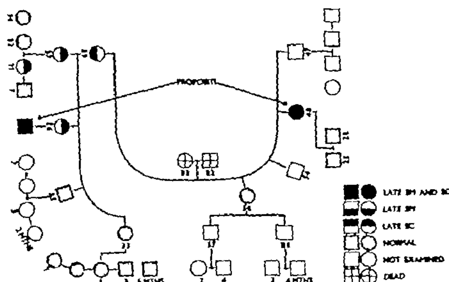


Fig. 9. Pedigree of Cases 2 and 3 showing the auscultatory features of 17 relatives. The causes of death of the 33-year-old woman and her 82-year-old husband are unknown.

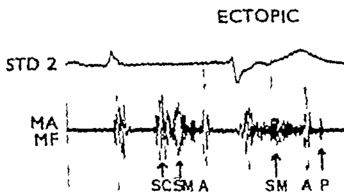


Fig. 10. Case 4. Nonejection systolic click and crescendo-decrescendo systolic murmur. The pansystolic nature of the murmur and the disappearance of the click are clearly demonstrated with the ectopic beat.

patients were examined and isolated nonejection clicks were found in 3 and a late systolic murmur in one. All 17 had normal electrocardiograms and chest x-ray films.

Case 4. An 8-year-old white girl was seen by her private practitioner in February 1964 for pain low in the back. Because a cardiac murmur was heard, she was referred to a pediatrician (Dr. H. L. Urbach) in Johannesburg for further investigation. She had no cardiac symptoms and there was no history of rheumatic fever.

Examination revealed an apical Grade 2 late systolic murmur and a late systolic click. Occasional ectopic beats occurred and the late systolic murmur then became pansystolic (Fig. 10). The chest radiograph was normal. The electrocardiogram showed elevated S-T segments, Q waves, and an inverted T in Leads II, III, and AVF (Fig. 11). On left ventricular cineangiocardiography a considerably dilated posterior mitral leaflet (Fig. 12) and mild mitral regurgitation were demonstrated.

In view of the high incidence of systolic clicks in the relatives of the two preceding patients, the available members of this child's family were also examined. Her father had an isolated mid-late systolic click, with no other abnormality. The father's sister and her four children were normal, however.

Case 5. This 17-year-old white boy was admitted to the Plastic Surgery Unit of this hospital in February 1963 for operation for a cleft palate. Because a heart murmur was detected, we were asked to assess his cardiac status prior to operation. He denied cardiac symptoms or past history of rheumatic fever. His mother had died suddenly at the age of 30 years of a weak heart. A brother 12

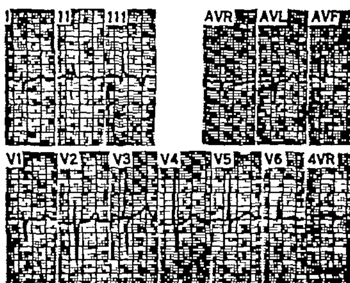


Fig. 11. Case 4. Electrocardiogram showing Q waves, elevated S-T segments, and inverted T waves in Leads II, III, and AVF.

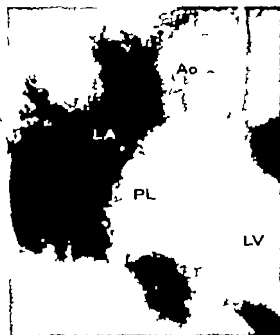


Fig. 12. Case 4. Right anterior oblique projection of the left ventricular cineangiocardiogram. Aneurysmal dilatation of the posterior leaflet (*PL*) is apparent.

years old, had died suddenly *after jumping* into a swimming bath. Another brother, 16 years old, was reputed to have a "leaking valve" and had recently been rejected for military service on account of this. Unfortunately, we have been unable to examine this subject ourselves.

Physical examination revealed low-set ears, a cleft palate, and harelip. A severe pigeon-chest deformity was present. There was no clinical evidence of cardiomegaly, but a loud nonejection systolic click and a Grade 3(6) late systolic murmur were heard at the apex (Fig. 13). X-ray examination showed that thirteen ribs were *present on both* sides, but the cardiac silhouette was normal.

The electrocardiogram of February, 1963, was very abnormal in that there was a deep Q and an inverted or diphasic T in Leads II, III, AVF, V_4, V_5, and V_6 (Fig. 14,*a*). Frequent ventricular ectopic beats were present. When another electrocardiogram was recorded in September, 1964, the T wave in Lead II had become upright, and the S-T segments and T waves in Leads AVF, V_4, V_5, and V_6 had a more normal shape (Fig. 14,*b*). The T waves in Leads V_2, V_3, and V_4 had become considerably taller.

Consent for cardiac catheterization was repeatedly refused. When the patient was last seen in September, 1964, he stated that he had experienced palpitations on exercise for the previous 6 months. Physical examination was unchanged. The ventricular ectopic beats were still present, and these increased in frequency during and after effort.

Discussion

Although to our knowledge all the features of this syndrome have not previously been correlated, there are several descriptions of identical or very similar cases in the recent literature.[7,8]

In their discussion of apical systolic murmurs, Humphries and McKusick[7] reported 11 cases of a "characteristic electrocardiographic-auscultation syndrome



Fig. 13. Case 5. Crescendo-decrescendo late systolic murmur and nonejection click.

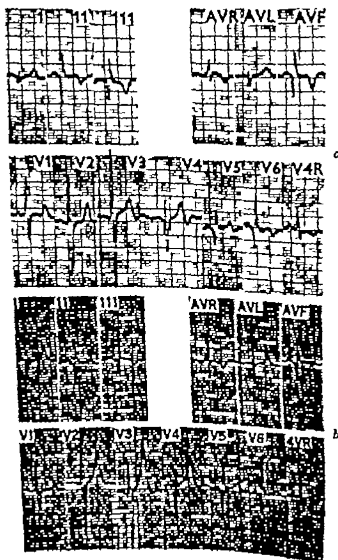


Fig. 14. Case 5. Electrocardiograms. a, February 1961. The tracing is very abnormal and shows deep [illegible] waves, abnormal S-T segments and negative or diphasic T waves in Leads II, III, AVF, V4, V5 and V6. b, [illegible] 1961. Improvement in the S-T segment and T-wave pattern is seen in Leads II, AVF, V4, V5 and V6. [illegible] and peaked T waves have developed in the mid-precordial leads.

in which a late systolic murmur was present on auscultation and electrocardiography showed a diphasic or inverted T wave in Standard Leads II and III with tall peaked T waves in the mid precordial leads. Some of their patients also had mid late systolic clicks, and several gave a history of anterior chest pain. Humphries and McKusick[7] stated that the condition mimics the syndrome of angina pectoris due to coronary insufficiency, but they regarded previous pericarditis as the likely explanation. Four of their patients had normal pressures at cardiac catheterization, but apparently none had been subjected to left ventricular cineangiocardiography. The same paper[7] describes the case of a symptomless man with a late systolic murmur and an electrocardiogram that was reputedly normal except for frequent premature ventricular contractions. Left ventricular cineangiocardiography showed a bulging of the posterior mitral valve leaflet in addition to late systolic mitral regurgitation. The cineangiocardiogram[7] (Figure 12a, page 165) is very similar to those of our 4 patients. The patient had been involved in an automobile accident 11 years earlier but had no recognized chest injury. The nature of the mitral valve deformity was not understood, although the possibilities of ruptured chordae tendineae or a congenital anomaly were entertained.

Rupture of chordae tendineae was also considered by Ross and Criley[9] in a 39-year old patient with a late systolic murmur and a "nonspecific T wave abnormality" on the electrocardiogram. The left ventricular cineangiocardiogram showed late systolic mitral regurgitation and ballooning of the posterior leaflet (Figure 9, page 213). This man gave no history of rheumatism, trauma, or severe infection and appears to have the same syndrome as our patients.

Similar auscultatory and electrocardiographic features were recently reported by Pocock and associates[8] in an 18-year old white boy. However, they interpreted his left ventricular angiocardiogram as showing a subvalvular aneurysm. We had also thought that the angiocardiographic appearances in our patients might be those of a subvalvular ventricular aneurysm until Criley,[10] who has seen the cineangiocardiograms of Cases 1 and 3, pointed out to us that the protrusion occurs during ventricular systole and empties completely during ventricular diastole. The cineangiocardiograms of Cases 2 and 4 are similar and there is now little doubt in our minds that it is the posterior leaflet which balloons and not a subvalvular ventricular aneurysm which fills.

The explanation of the electrocardiographic changes is uncertain. The elevated S-T segments and T wave inversion in Leads II, III, and AVF and sometimes also in the lateral chest leads, are compatible with posteroinferior myocardial ischemia or infarction. The tall T waves which occurred in Leads V_2-V_4 in our Cases 2, 3, and 5, in the young man reported by Pocock and associates,[8] and in several of Humphries and McKusick's patients[7] are also compatible with this interpretation. Even if posterior myocardial damage is accepted, however, its relationship to the valvular abnormality remains difficult to explain.

One possibility would be that ischemia or congenital anomaly of the posteromedial papillary muscle results in dysfunction of this papillary muscle analogous to the recently recognized anterolateral papillary muscle dysfunction syndrome.[11-13] Such dysfunction of the posteromedial papillary muscle could result in a systolic click because of the abnormal tension on or elongation of the chordae tendineae arising from that muscle, and could later result in mild mitral regurgitation. If, in fact, elongation of the chordae does occur, this might allow the valve leaflet to bulge and, as with any other aneurysm, this could be progressive.

On the other hand, the isolated systolic clicks and, in one instance, the late systolic murmur found in relatives with normal electrocardiograms of 3 of our patients suggest that the chordal and leaflet abnormalities occur first. In the absence of anatomic material, it is not clear why massive dilatation of the posterior leaflet should result in, or be associated with, posteroinferior myocardial injury, ischemia, or infarction. Perhaps the dilated posterior leaflet, even though inside the left atrial cavity, can either by direct

pressure or by a movement of the mitral annulus, distort the circumflex coronary artery as it runs behind the left atrium in the atrioventricular groove. Such distortion could then cause occlusion or thrombosis of this vessel and produce posterior myocardial ischemia. This postulate would explain more satisfactorily the myocardial damage in the very young patients than would the theory of primary myocardial pathology. It is also compatible with the histories of chest pain or palpitations in 3 of our patients (Cases 1, 2, and 5), in the young man reported by Pocock and associates,[8] and in some of Humphries and McKusick's[7] patients with the specific electrocardiographic-auscultatory syndrome.

The case reported by Segal and associates[14] of a 16-year-old girl with Marfan's syndrome and a late systolic murmur in whom cineangiocardiography confirmed the presence of mitral regurgitation is relevant to this discussion. Her electrocardiogram 5 years earlier[14] (Figure 4b, page 460) showed T wave and S-T segment changes in Leads II, III, AVF, V_5, and V_6 identical to those which we have discussed. The most recent electrocardiogram[14] (Figure 4a, page 459), however, indicated that these changes had virtually returned to normal. The electrocardiograms of 3 of our 5 patients have also shown improvement over the course of time. The T waves in Standard Lead II of Cases 2 and 5 have become upright, and the T waves and S-T segments in Leads AVF, V_4, V_5, and V_6 in Case 5 have now a more normal shape (Fig. 14,*b*). The electrocardiogram of Case 3 has also become more normal when compared with that recorded 12 months previously.

S-T segment and T wave abnormalities in Leads II, III, and AVF in 5 patients with Marfan's syndrome and mitral valve deformity have been discussed by Bowers.[15] Although necropsies were performed in all instances, and abnormalities of the mitral leaflets or chordae were mentioned, the detailed pathology was not described and the electrocardiographic changes were unexplained. McKusick,[1] when discussing the cardiovascular aspects of Marfan's syndrome stated that the condition of the chordae is often difficult to evaluate at necropsy, but he postulated that redundancy of chordae was present in some instances. Our study[4] of late systolic murmurs and nonejection systolic clicks includes 3 patients with Marfan's syndrome. One has an isolated systolic click, whereas *the others have a click and late systolic* murmur. The electrocardiograms in all are normal. Cineangiocardiograms have not been obtained, but we believe that mitral regurgitation is present in the 2 patients with murmurs. None of the 5 patients whose cases are at present under discussion nor any of their relatives who were examined showed features of Marfan's syndrome. The possibility remains, however, that the pathology of the mitral valve is similar in the two entities and that myocardial damage results directly from dilatation of the posterior mitral leaflet.

Whereas the presence of a late systolic murmur and a mid late systolic click has hitherto been regarded as either "innocent,"[17-20] extracardiac in origin,[7,21-23] or representative of only a mild hemodynamic abnormality,[1,2,22,24-26] the prognosis for subjects exhibiting electrocardiographic changes must at present remain guarded. The electrocardiogram in Case 5 suggests severe myocardial injury, and it is possible that the patient's 30-year-old mother and 12-year-old sibling died as a result of similar pathology. A history of chest pain and palpitations, which occurred in 3 of our patients (Cases 1, 2, 5), is compatible with myocardial damage and, thus, ventricular fibrillation might well be a danger.

To date, we have distinguished patients with this syndrome from others with similar auscultatory findings mainly by the abnormal electrocardiograms. Although the cineangiocardiographic appearances of the posterior leaflet have been a prominent feature, it is probable that left ventriculography in patients with late systolic murmurs but normal electrocardiograms would in many instances also reveal some billowing of that leaflet. Mobile and billowing posterior leaflets were certainly apparent in the 9 such patients so examined by us,[4] although the extent of the protrusion was considerably less than in the 4 patients whose cases (Cases 1-4) are described in the present report. We think that a similar appearance is illustrated

(Figures 3 and 4 page 760) in the recent report by Segal and Likoff[14] on 8 patients with late systolic murmurs and reputedly normal electrocardiograms. Electrocardiographic changes probably supervene, therefore when there is a severe degree of leaflet *billowing* The *presence of a billowing* posterior leaflet in patients with normal electrocardiograms also provides further evidence that the valve anomaly precedes the myocardial damage

All of the late systolic murmurs which we have recorded on a New Electronic Products (N E.P) multichannel phonocardiographic apparatus have had a crescendo-decrescendo shape.[4] Consequently we have not been able by this means to differentiate our 5 patients with electrocardiographic signs of posteroinferior ischemia from other patients with apical late systolic murmurs. Furthermore, the responses of the murmurs and clicks to the inhalation of amyl nitrite, a Valsalva maneuver and the injection of phenylephrine have been of similar pattern whether electrocardiographic abnormalities were or were not present.[1,2,4,5] The point of maximal intensity of late systolic murmurs has ranged in our experience [2,4] from the middle of the murmur to very near the end In the latter instance the murmur has been slowly crescendo until shortly before aortic closure, and then rapidly decrescendo, finishing on or immediately after the aortic component of the second sound Segal and Likoff[14] who used a direct writing Schwarzer apparatus, considered that the late systolic murmur of mitral regurgitation is crescendo to the second sound but they have regarded the diamond-shaped late systolic murmur and especially that initiated by a systolic click, as innocent. It appears to us to be impossible that any intracardiac murmur could have only a crescendo component unless it is abruptly terminated by closure of a valve as occurs for example with the crescendo presystolic murmur of mitral stenosis. Clearly there is no valve closure that could interrupt a systolic murmur of mitral regurgitation and we believe that every late systolic murmur must have a decrescendo component, even if this is very rapid on some occasions.

Neither apical late systolic murmurs nor nonejection systolic clicks are a common auscultatory finding in routine cardiological practice, so that the comparatively high incidence of these signs in the relatives of our patients is very suggestive of an hereditary factor sometimes being involved in the anomaly of the mitral valve *mechanism* *Under such circumstances* we postulate that there is a genetically determined defect or weakness of the posterior leaflet, which may ultimately billow or develop aneurysmal dilatation In only one of our 5 cases (Case 1) was there no apparent familial factor but we do not intend to imply that the mitral valve anomaly is invariably congenital Massive protrusion of the posterior leaflet was not observed in the other 9 patients with late systolic murmurs on whom cineangiocardiograms have been recorded [2] although in all instances that leaflet appeared to be very mobile, and in some it billowed fairly prominently It is possible that patients showing electrocardiographic signs of posteroinferior ischemia will be encountered in whom the pathology of the mitral valve is secondary to rheumatic or other causes. The patient with Marfan's syndrome described by Segal and associates[14] is such an example.

The quadruple rhythm in Case 1 provided an observation which is relevant both to the mechanism of gallop sounds and the pathology of the mitral valve in *this* syndrome. The timing of the *atrial* sound (F-G interval 0 16 second) was in no way unusual [4] but the third heart sound occurred extremely late, with an A-3 interval of 0 24 second The A 3 interval usually falls between 0 10 and 0 20 second [17] and we cannot recall having previously encountered a third heart sound of such delayed onset in either a normal or a pathologic heart Nixon[18,19] has recently disputed the view that the third heart sound has a muscular origin and has postulated that it is caused by tensing of the mitral valve leaflets and chordae tendineae at the time of ascent of the annulus fibrosus. Rodin and Tabatznik[19] have shown that the A 3 interval can be lengthened by a decreasing venous return which alters the state of distention of the ventricle in diastole and their observation is still compatible with the valvular theory of production of the third sound It would be logical

to assume, however that if the chordae were abnormally long and lax as seems to be likely in our patients, then the slack would be taken up later than usual and consequently the onset of the third heart sound would be delayed.

Summary

In previous communications, evidence has been produced that apical late systolic murmurs are invariably due to mitral *regurgitation, and that the commonly as*sociated nonejection systolic clicks result from abnormalities of the mitral chordae tendineae. The present paper describes 5 patients with both of these auscultatory findings who had in addition electrocardiographic signs compatible with posteroinferior myocardial ischemia or infarction Left ventricular cineangiocardiography was performed in 4 of the 5 patients, and an aneurysmal dilatation of the posterior leaflet of the mitral valve was demonstrated

It is postulated that distortion of the circumflex coronary artery by the abnormal mitral valve may be the cause of the electrocardiographic features. The probability is briefly discussed that in some instances the mitral valve anomaly results from a genetically determined defect, or weakness, of the posterior leaflet.

We are extremely grateful to Dr J M Criley of Johns Hopkins Hospital, Baltimore, Maryland for his help with the interpretation of the left ventricular cineangiocardiograms. Discussions with Dr Criley were made possible by the award to one of us (J.B.B.) of a Wellcome Research Travel Grant in 1964 We are indebted to Dr H L Utian and Dr A. B. Nel for allowing us to include Case 4 in this series. Dr R. Glyn Thomas recorded the cineangiocardiogram on that patient and kindly gave us access to it. We wish to thank Miss Faye Simpson for considerable assistance in the preparation of this paper and Dr C. J van Wyk, Superintendent of the Johannesburg General Hospital, for permission to publish

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Mechanical destruction of erythrocytes by incompetent aortic valvular prostheses

Clinical, hemodynamic, and hematologic findings

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The development of prosthetic devices for complete replacement of the aortic valve has provided the surgeon with effective means for correcting both stenotic and regurgitant malformations which are not amenable to reconstructive procedures. The prosthetic valves which first gained wide acceptance were constructed of flexible Teflon fabric, either as individual leaflets[1] or as tricuspid facsimiles of the normal aortic valve.[2] At the National Heart Institute, such flexible Teflon prostheses were used for replacement of the aortic valve between 1961 and early 1963 and a detailed description of the clinical and hemodynamic consequences of their application has been presented elsewhere. The initial function of the Teflon valves was satisfactory but later fracture of the fabric caused severe aortic regurgitation in the majority of patients. More recently the caged-ball valve devised by Starr and associates[4] has been found to be preferable to the flexible valves, and it is now employed when replacement of the aortic valve is indicated.

In this total surgical experience, comprising more than 150 patients, an unusual postoperative sequel was documented in 5 patients who developed aortic regurgitation after replacement of the aortic valve. Each of them became anemic and evidenced severe intravascular hemolysis. On detailed study the principal hematologic abnormality was shown to be mechanical destruction of erythrocytes by the prosthesis. The clinical and laboratory findings in these 5 patients, the effects of secondary operative treatment in them and mathematical considerations of the effects of regurgitant blood flow on the frequency of cell trauma are presented in the report which follows.

Clinical summaries

Case 1. W. L., a 48-year-old engineer entered the National Heart Institute in January 1962, with a history of progressive angina, exertional dyspnea, orthopnea, and peripheral edema. The electrocardiogram, chest roentgenograms, and cardiac catheterization confirmed the clinical diagnosis of combined aortic stenosis and regurgitation. The hematocrit was 43 per cent. The aortic valve was replaced with

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a tricuspid Teflon prosthesis of the Muller type.[8] The patient's postoperative course was uncomplicated and the hematocrit at discharge was 38 per cent.

Seven months postoperatively a diastolic murmur was audible and cardiac catheterization confirmed that moderately severe aortic regurgitation was present (direct brachial arterial pressure, 108/42 mm. Hg). The hematocrit was 43 per cent at this time and the patient was asymptomatic. He continued to be well until 15 months after operation when he developed weakness, angina, exertional dyspnea, and epigastric pain. The direct arterial pressure was 110/40 mm. Hg, the hematocrit was 35 per cent, and the hemoglobin was 11.1 Gm. per 100 c.c. Although roentgenographic examinations suggested a chronic duodenal ulcer, no occult blood was present in the stools.

At home the patient did poorly, with increasing weakness, poor appetite, and loss of weight. His hemoglobin fell to 6.6 Gm./100 c.c. and he was given blood transfusions by his physician, who also noted hemoglobinuria. On readmission to the Institute 18 months postoperatively, the physical findings were unchanged, except that scleral icterus was evident. The hematocrit was 32 per cent, and the hemoglobin was 9.9 Gm./100 c.c. The prothrombin time was normal, as was the silicone clotting time. Reticulocyte counts ranged from 4.4 to 7.2 per cent. Urinalysis showed massive hemoglobinuria, 1+ protein reaction, and hemosiderin was present in moderate amounts. The total serum bilirubin was 2.0 mg./100 c.c., with 0.71 mg./100 c.c. direct component. The only abnormal liver function test was a serum glutamic oxalacetic transaminase of 90 units. Serum iron was 98 μg/100 c.c., and the total iron binding capacity was 288 μg/100 c.c. Fecal urobilinogen excretion was 449 mg./24 hours. Direct and indirect Coombs tests, cold and acid hemolysin, urinary FIGLU excretion, erythrocyte methemoglobin, glucose-6-phosphate dehydrogenase, and hemoglobin electrophoresis determinations were normal. Erythrocyte osmotic fragility was slightly increased after incubation. A biopsy of bone marrow revealed erythroid hyperplasia. The peripheral blood smear demonstrated numerous fragmented erythrocytes (schistocytes) (see Fig. 1). The survival of Cr^{51}-tagged red cells was grossly reduced, their average half-life being 9.5 days (Fig. 2).

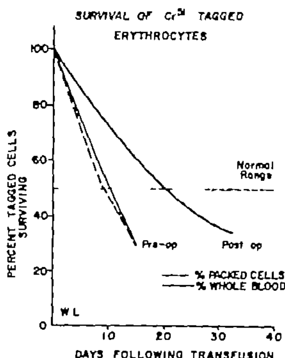


Fig. 2. Erythrocyte survival curves determined in Patient W. L. while an incompetent flexible Teflon valve was present (*Pre-op*) and 90 days after it had been replaced by a Starr-Edwards valve (*Post-op*). At both times, a stable anemia is indicated by the similar rates of decline in the radioactivity of whole blood and packed cells. The slightly decreased cell survival evident postoperatively is characteristic of the effect of a competent caged-ball prosthesis.[12]



Fig. 1. Peripheral blood smear of Patient W. L. Numerous fragmented erythrocytes (schistocytes) are evident; several are indicated by arrows.

In October, 1961, the Teflon prosthesis was excised and replaced with a Starr-Edwards valve. The Teflon prosthesis was stiffened, the edges were rolled, large perforations were present in all three leaflets, and the fabric had not been covered with endothelium (Fig. 3). Postoperatively, the patient's course was uneventful. Hemoglobinuria was never evident after operation, and at discharge the hematocrit was 43 per cent, the reticulocyte count was normal, as were all previously abnormal hematologic and chemical studies. Erythrocyte survival was determined 3 months postoperatively and this curve is also shown in Fig. 2. The average half-life had increased to 21 days.

Case 2. C. P., a 44-year-old housewife, had rheumatic heart disease and closed mitral and aortic valvulotomies had been performed at another hospital 6 years before her admission to the Institute in November, 1961. Clinical and hemodynamic studies indicated recurrent or residual stenosis of both valves. The hematocrit was 49 per cent and other pertinent laboratory examinations were normal. In January, 1962, the aortic valve was replaced



Fig. 3. The flexible Teflon prosthesis removed at reoperation in Patient W.L. All three leaflets are perforated, and nodular calcific deposits are apparent, particularly on the leaflet at the right of the photograph.

with a Muller Teflon prosthesis, and a transventricular mitral commissurotomy was also performed. The patient's recovery was smooth, and the hematocrit at the time of discharge was 39.5 per cent. Postoperative studies in August, 1962, and March, 1963, showed progressive stenosis of the prosthesis but no significant aortic regurgitation. The hematocrit was normal on both occasions. In December 1963, however, she developed fatigability and ascites and was readmitted. Her physician had noted anemia in the preceding month and had treated her with parenteral iron. She had also had dark urine, and on examination she was mildly jaundiced. Murmurs of aortic stenosis and regurgitation were audible. The hematocrit was 36 per cent, reticulocyte counts ranged from 2.5 to 7.4 per cent, platelets were 188,000 per cubic millimeter and the leukocyte count was 4,900 per cubic millimeter with a normal differential cell count. Serum iron was 75 μg/100 c.c. and total iron binding capacity was 335 μg/100 c.c. Direct and indirect Coombs test, osmotic fragility and hemoglobin electrophoresis were normal. Fecal urobilinogen excretion was elevated, 268 mg./24 hours. Hemoglobin and hemosiderin were present in the urine. Examination of bone marrow showed erythroid hyperplasia. Survival of Cr^{51}-tagged erythrocytes revealed a *half-life of 14 days* (Fig. 4). Since the hemolytic anemia was compensated and the patient responded well to a cardiotonic regimen, she was discharged.

Six months later in June, 1964 she was again admitted because of severe cardiac failure. The hematocrit was 36 per cent reticulocytes 6.2 per cent, total serum bilirubin 2.9 mg./100 c.c. and the plasma hemoglobin 95 mg./100 c.c. The Teflon aortic valve was replaced with a Starr Edwards valve, but the patient died of left ventricular failure 12 hours after operation. The Teflon prosthesis was calcified and there were several large perforations in the leaflets. Its appearance was similar to the valve illustrated in Fig. 3.

Case 3. F. R., a 47-year-old man, entered the National Heart *Institute* in November 1961 because of increasing exertional dyspnea and syncopal episodes. The electrocardiogram, chest roentgenograms, and cardiac catheterization confirmed the physical findings of combined aortic stenosis and regurgitation. Preoperatively the hematocrit was 44 per cent. The aortic valve was excised and re-

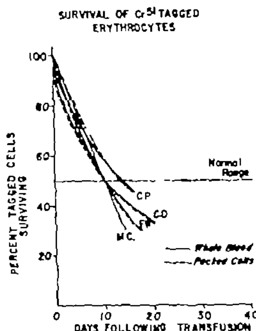


Fig. 4. Erythrocyte survival curves of 4 patients with incompetent prosthetic aortic valves. Patient C.O. has regurgitation around a Starr-Edwards valve, whereas the others all had flexible Teflon valves. As in Patient W. L. (Fig. 2) the radioactivity of whole blood and that of packed cells decline at similar rates.

placed with a tricuspid Teflon prosthesis of the Muller type. Postoperatively there was no evidence of aortic regurgitation, and the hematocrit was 40 per cent.

The patient was readmitted in July 1962 March, 1963 and October 1963. At each admission the hematocrit was normal, but serial cardiac catheterizations revealed an increasing systolic gradient across the Teflon prosthesis and a progressive rise in the left ventricular end-diastolic pressure. A diastolic murmur was heard for the first time in October 1963, and 1 month later he suddenly de-

veloped congestive heart failure and severe anemia.

At readmission November 1963 the diastolic murmur was much louder and the liver was palpable 8 cm. below the right costal margin. A striking increase in heart size was demonstrated by chest roentgenograms. The hematocrit ranged from 32.5 to 36.5 per cent, and the reticulocyte count from 6.3 to 7.9 per cent. The leukocyte count was 7,000 per cubic millimeter with a normal differential cell count. There was hemosiderin, a trace of bile, but no hemoglobin in the urine. Liver function studies were normal, except for a total serum bilirubin of 1.9 mg./100 c.c. Fecal urobilinogen excretion was 240 mg./24 hours. Serum iron was 32 μg/100 c.c., and the total iron binding capacity was 372 μg/100 c.c. Direct and indirect Coombs tests, urinary FIGLU excretion, glucose-6-phosphate dehydrogenase, and osmotic fragility tests were normal. A biopsy of the bone marrow revealed erythroid hyperplasia. Erythrocyte survival was distinctly shortened, the half-life of tagged red cells being 10 days.

An attempt was made to replace the Teflon *prosthesis, but at operation the aorta tore when* sternotomy was performed and the patient died of massive bleeding. The prosthesis was fragmented, its edges were rolled and it was not covered with endothelium.

Case 4. M.C., a 33-year-old woman, entered the National Heart Institute in March, 1962 because of progressive cardiac decompensation characterized *by angina pectoris, orthopnea, and peripheral edema.* On physical examination, the murmur of aortic stenosis was heard, and a peak systolic gradient of *160 mm. Hg across the aortic valve was demon*strated at cardiac catheterization. Laboratory studies preoperatively showed a hematocrit of 43.5 per cent, and other chemical and hematologic studies were normal, except for serum alkaline phosphatase of 13 King-Armstrong units. At operation a stenotic bicuspid aortic valve was replaced with two Teflon leaflets. There were no postoperative complications, but a repeat cardiac catheterization prior to discharge revealed a residual systolic gradient across the prosthetic leaflets of 91 mm. Hg.

In January, 1963 the patient was admitted to another hospital because of persistent anemia. An aortic systolic murmur and a blowing diastolic murmur were heard at that time. The liver was palpable 3 cm. below the right costal margin and was *not pulsatile. The hematocrit was 30 per cent,* hemoglobin 9.8 Gm./100 c.c., and the reticulocyte count 3.2 per cent. Fecal urobilinogen excretion was 441 mg./24 hours. Direct and indirect Coombs tests were negative. All liver function studies were normal, except for cephalin flocculation of 4+ and a prothrombin time of 68 per cent. Liver biopsy was normal; the bone marrow showed erythroid hyperplasia. The erythrocyte survival curve is shown in Fig. 4; the half-life of tagged cells was 10.5 days. The patient was discharged without specific therapy.

The sudden onset of pulmonary edema necessitated admission of the patient to her local hospital in June, 1963. Again, the murmurs of aortic stenosis and regurgitation were audible. The liver was palpated at the umbilicus, was pulsatile, and the patient was markedly jaundiced. The hematocrit was 30 per cent, hemoglobin was 8 Gm./100 c.c., and the leukocyte count was 14,000 per cubic millimeter *with 89 per cent neutrophils. The urine contained* both bile and protein; the total serum bilirubin was 9.8 mg./100 c.c. Pulmonary edema persisted despite therapy; the serum bilirubin rose to 30.4 mg./100 c.c., and the serum alkaline phosphatase rose to 11.6 King-Armstrong units on the seventh hospital day. The patient died on the eleventh hospital day, and the two Teflon leaflets removed at autopsy were found to be not only torn but quite rigid. They were not endothelialized.

Case 5. C.O., a 38-year-old grocer, had calcific aortic stenosis, and in March, 1963 the aortic valve was replaced with a Starr-Edwards prosthesis. The *preoperative hematocrit was 48 per cent. No mur*murs were audible in the immediate postoperative period, but on the fourth day a diastolic murmur along the left sternal border became audible. The hematocrit was 32 per cent at the time of his discharge 2 weeks postoperatively.

The patient returned for routine re-evaluation 14 months after operation. He described good *symptomatic improvement, but the diastolic mur*mur was still present and the direct brachial arterial blood pressure was 140/35 mm. Hg. The hematocrit was 39 per cent and the reticulocyte count was 2.4 per cent. Schistocytes were present in the peripheral blood smear, but no hemoglobin or hemosiderin was detected in the urine. Serum iron was 75 μg/100 c.c. and the total iron binding capacity was 266 μg/100 *c.c. All liver function studies were normal; no im*munologic or enzymatic basis for erythrocyte destruction could be established. The half-life of Cr^{51}-tagged erythrocytes was 12 days (Fig. 4). The patient remains well, there has been no increase in the severity of his aortic regurgitation, and his anemia remains well compensated.

Comment

All of the 5 patients described in this paper presented the clinical findings of aortic regurgitation through or around a prosthetic aortic valve and, in addition, were anemic. Appropriate studies were *carried out to determine whether the* anemia was immunologic or enzymatic in origin, and these mechanisms were excluded. Further investigation led to the conclusion that intravascular hemolysis was taking place, which was supported by the findings of hemoglobinemia, hemosiderinuria, elevated levels of plasma hemoglobin, and erythroid hyperplasia of the *bone marrow. Accelerated destruction of* erythrocytes was then proved in each patient when the survival time of tagged red blood cells was determined and found to be grossly decreased. Further evidence indicative of intravascular destruction of erythrocytes was obtained in the 3 patients in whom whole body radioactivity

and also counts over the liver and spleen were recorded in the course of the Cr^{51}–red cell survival studies. In them there was a concentration of radioactivity over the liver a finding which is consistent with intravascular hemolysis.[6]

Although all of the patients were anemic, they compensated well for the increased rate of destruction of red cells In each, the hematocrit was 30 per cent or greater and a reticulocyte count above 8 per cent was never observed. In 4 patients the radioactivity of whole blood and of red cells decreased at the same rate, indicating that cell destruction and cell production were occurring at similar rates.[6] In this connection, it must be emphasized that the indication for the secondary operations performed in 3 patients was not anemia but congestive heart failure due to aortic regurgitation.

Several previous reports have described postoperative hemolytic anemia in patients in whom incomplete persistent atrioventricular canal was corrected by suture of the cleft anterior mitral valve leaflet and reconstitution of the interatrial septum with a Teflon fabric prosthesis. In the patient described by Sayed and associates[7] and in the 2 reported on by Verdon and associates,[8] residual mitral regurgitation was found to be present and in addition a portion of the Teflon fabric on the left side of the interatrial septum was not covered with endocardium. In these patients it was postulated that the destruction of red cells resulted from direct trauma, inflicted upon the cells when the regurgitant jet of blood from the left ventricle struck the bare fabric. Similar hematologic findings were present in the 2 patients described by Sigler and associates,[9] but at reoperation the fabric was found to be smoothly covered with endocardium and residual mitral regurgitation alone appeared to have been responsible for the destruction of erythrocytes. In considering the specific mechanism of cell destruction, Sigler concluded that turbulent blood flow and shearing forces, resulting from increased and rapidly changing velocity and pressure, were principally responsible Stohlman and associates,[1] in their studies of ball-valve prostheses in the dog also called attention to the importance of shearing forces and rapidly changing pressures in causing the destruction of red cells. Fok and Schubothe[11] traumatized red cells in vitro by rolling them in a flask containing quartz beads. They concluded that simple mechanical crushing of the cells was not the means by which they were destroyed and also implicated surface forces as the principal mechanism of hemolysis. This conclusion is reinforced by the recent clinical observations of Brodeur and associates,[12] who demonstrated a decreased survival of red cells preoperatively in 15 patients with aortic stenosis or regurgitation.

Many other congenital or acquired cardiovascular malformations are associated with increased velocity and turbulence of blood flow e g patent ductus arteriosus aortopulmonary septal defect ruptured sinus of Valsalva aneurysm and mitral regurgitation. These lesions, and their hemodynamic consequences, have been familiar to physicians for many years but there have been no descriptions of hemolytic anemia in association with them The findings in the present study and in that reported by Brodeur and associates, would suggest that detailed hematologic evaluations in patients with these and other malformations might prove to be of interest

The Teflon valvular prostheses removed at operation or autopsy in the patients described above exhibited similar morphologic changes, typified by the valve illustrated in Fig 3 In all the leaflets were stiffened had tears or perforations in them and the margins of the perforations as well as the leaflets had nodular calcific deposits on them. In addition portions of the prosthetic leaflets were not covered by endothelium or fibrous tissue Although bare Teflon was present, it would appear that the same hemodynamic factors suggested by Sigler were of primary importance in the destruction of red cells. Velocity of flow was greatly increased as in any patient with aortic regurgitation and the grossly irregular surfaces small orifices, and the calcific nodules on the valves caused critical turbulence and shearing This mechanism is also apparently responsible for the destruction of red cells in Patient C O in whom regurgitation exists around the fixation ring of a Starr Edwards ball valve This patient had extremely dense calcifica

tion of the aortic annulus, and the deposits extended into the left ventricular myocardium as well. It was necessary, therefore, to place a number of the sutures fixing the valve into residual calcium, and the regurgitant orifice undoubtedly occurred when one or more of them tore through in this area. Since reoperation seems to be unnecessary, it has not been determined whether bare Teflon is present, but the regurgitant flow is almost certainly through a tract lined, at least in part, by calcific deposits.

Mechanical destruction of erythrocytes by a patient's diseased valve or by a prosthetic valve is more severe when the valve becomes grossly incompetent. For example, 3 of the present patients had no evident hemolysis early in their courses when aortic regurgitation was mild, and anemia became manifest only when valvular insufficiency became severe enough to cause cardiac decompensation. Also Marsh[13] and Stevenson and Baker[14] have recently reported on 4 patients with hemolytic anemia after the insertion of Starr-Edwards aortic valves; in each patient, regurgitation *around* the prosthesis was present. This clear association of aortic regurgitation and the mechanical destruction of erythrocytes may be explained by a consideration of the effects of regurgitant flow upon the frequency with which cells are subjected to trauma. Mathematically, the relationship between the severity of regurgitation and the number of times a *regurgitated* cell passes the valve can be expressed in the following formula, which is derived in the appendix:

$$A_{(p)} = \frac{3 - p}{1 - p}$$

where p = porportion of regurgitation $\left[\frac{\text{regurgitant volume}}{\text{total forward stroke volume}}\right]$ and $A_{(p)}$ = average number of times a regurgitated cell passes a fixed point. The probability of any ejected cell being regurgitated is determined by the proportion of the stroke volume regurgitated, p; the probability that a cell will not be regurgitated is 1 − p and a nonregurgitated cell will pass the valve only 1 time. Thus the average number of times that any ejected cell will pass

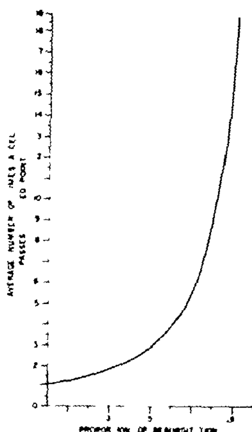


Fig. 5. The relationship of the magnitude of regurgitant blood flow to the average frequency with which a cell is traumatized (Tp). The proportion of regurgitation (p) is the fraction of total forward stroke volume which regurgitates in the succeeding diastole. The formula from which the curve was constructed, and its derivation, are presented in the text and appendix.

the valve, Tp, may be expressed by the sum of the passages of regurgitated and nonregurgitated cells:

$$T = \left[p \times \frac{3 - p}{1 - p}\right] + (1 - p).$$

If this equation is solved for various values of p and they are plotted against p, the curve shown in Fig. 5 is obtained. It is apparent that small increases in the severity of regurgitation after 0.5 result in striking increases in the average number of times a cell is traumatized. Thus, with relatively mild regurgitation (p = 0.2), a cell will theoretically contact the valve an average of only 1.5 times before it finally enters the systemic circulation. With more severe regurgitation (p = 0.70), a cell will pass the valve an average of 5.7 times before

final ejection The value of 70 per cent regurgitation is not an unrealistic one since recent direct measurements of the magnitude of regurgitant flow in patients operated upon for aortic regurgitation have revealed regurgitant fractions ranging from 63 to 75 per cent of total left ventricular stroke volume.[18] Also, the theoretical considerations above do not take into account the greatly augmented stroke volume which accompanies aortic regurgitation This results in an increase in the absolute number of cells regurgitated and traumatized and therefore, makes hemolysis even more severe.

Summary

The clinical hemodynamic, and hematologic findings are described in 5 patients in whom severe intravascular destruction of erythrocytes resulted from incompetent prosthetic aortic valves. In each an enzymatic or immunologic bases for anemia was excluded, and grossly attenuated survival of Cr^{51} labeled red cells was demonstrated Destruction of erythrocytes was attributed to turbulent flow and shearing forces rather than to direct mechanical impact. In 1 patient, the half life of tagged cells increased from 9 5 to 21 days after an incompetent Teflon valve was replaced with a prosthesis of the caged ball type. The magnitude of regurgitant blood flow is an important determinant of the frequency with which a cell is subjected to trauma and the derivation and application of a formula relating these variables is presented

Appendix

If p is the proportion of any ejected volume that is regurgitated then p is the probability that an individual cell is regurgitated The probability that an individual cell is not regurgitated is $1 - p$. It is assumed that p is constant and $0 \leq p \leq 1$ The probability that a cell is regurgitated n times where $0 \leq n \leq \infty$ is p^n The probability that a cell is regurgitated exactly n times (i.e. not regurgitated after the $(n+1)^{th}$ time) is $p^n(1-p)$ The probability that a cell is regurgitated exactly n times, given that it has been regurgitated at least r times is

$$\frac{p^n(1-p)}{p^r}$$

which equals $p^{n-r}(1-p)$ It is assumed that $0 \leq r \leq n$ The average number of regurgitations given at least r regurgitations, is obtained from

$$\sum_{n=r}^{\infty} np^{n-r}(1-p).$$

Setting $n - r = m$ this may be written

$$\sum_{m=0}^{\infty} (m+r)\,p^m(1-p)$$

$$= \sum_{m=0}^{\infty} mp^m(1-p) + r\sum_{m=0}^{\infty} p^m(1-p) = \frac{p}{1-p} + r$$

With each regurgitation a cell crosses a fixed point twice, since regurgitation must be preceded by ejection. Therefore, $A_{(\ )}$ the average number of times a regurgitant cell crosses a fixed point, can be expressed by the equation

$$A_{(n-r)} = 2\left[\frac{p}{1-p} + r\right] + 1$$

Note that 1 must be added to the formula to account for the last time the cell is expelled without being regurgitated To consider cells which have been regurgitated at least once, r is set at 1 Therefore we obtain

$$A_{(1)} = 2\left[\frac{p}{1-p} + 1\right] + 1$$

$$= 2\left[\frac{p+1-p}{1-p}\right] + \left[\frac{1-p}{1-p}\right]$$

$$= \frac{3-p}{1-p}$$

The authors wish to thank Mrs Barbara Reis, Miss Joan Gurian and Dr Robert W Berliner for their help in deriving the formula relating regurgitant flow to the frequency of cell trauma. Dr George Brecher Dr Richard K. Wertz, and Dr William R. Bronson, of the Hematology Section, Laboratory of Clinical Pathology performed the hematologic studies and assisted in interpreting them.

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Heart size and prognosis in myocardial infarction

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Comment in the medical literature on heart size and the part it plays in and after an acute myocardial infarction is contradictory. *A Textbook of X-Ray Diagnosis by British Authors*[1] in 1962, mentions Parkinson's investigations[2] of 1936. In a series of 200 cases of cardiac infarction there were 128 with enlargement of the heart. The size of the heart after infarction bears no relation to the ultimate prognosis, life-expectancy being equal whether the heart is large or small." In Palmer's series,[3] enlargement was found in 64 per cent, and a decided superiority (39 over 23 per cent) in the ability to work was evident in the group with the normal heart size over the group showing enlargement. Patients with large hearts lived almost as long as those with hearts of normal size.

Bjerkelund[4] stated that the mortality rate increased with increasing heart volume among patients with myocardial infarction. Amundsen[5] came to the conclusion that in coronary disease a relationship exists between the relative volume of the heart and the prognosis. A decrease occurred in the survival ratio from small relative volumes to large relative volumes.

Little information is thus available on the significance of heart size to the prognosis. The present paper attempts to throw additional light on whether there is a difference between the life-expectancy of patients whose relative heart size in connection with the first attack of myocardial infarction is found to exceed the normal, and the life-expectancy of patients with normal heart size. An attempt has also been made to define the clinically observable factors which may contribute to enlarging the hearts of some but not all patients.

The series

The series comprised 125 patients, 26 women and 99 men, treated in 1956-1958 in the South Saimaa Central Hospital for their first myocardial infarction. The diagnosis was based on symptoms, clinical picture, and typical electrocardiographic and laboratory findings (elevated serum glutamic oxalacetic transaminase, erythrocyte sedimentation reaction, and leukocyte count). Uncertain and borderline cases were not included. Patients with a relapse of infarction were excluded, as were those who besides the coronary disease suffered from congestive heart failure, congenital

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or acquired heart defects, or diseases which could before the infarction have affected the size of the heart Hypertension however was not taken to be an excluding factor Patients who had been treated for or had a history of symptoms and/or signs of congestive heart failure were excluded Those who developed congestive failure after the acute infarction during hospitalization or later were included

From the number of patients so obtained those who were discharged from the hospital as convalescents and who survived for not less than 1 month afterward, formed the present series The patients were subjected to radiography in their fourth week of recovery in order to determine the size of their hearts according to the method of Liljestrand and associates,[6] with the patient in standing position during the exposure The experimental error involved in this method is, according to various authors, slightly below 5 per cent[7,8] Amundsen[8] states that the error of the method was about 30 ml per square meter and when one observer carried out the examination the true heart volume would be the recorded volume ± 60 ml per square meter In the present study the films were always read by the same radiologist (E H) In blind double determinations the differences in 22 volume readings ranged from 0 to 40 ml thus the standard deviation was ± 13 32 and its standard error was ± 8 96 ml per square meter

The relative heart size was taken to be normal if the volume for women was 300 to 450 ml per square meter and for men 350 to 529 ml. per square meter Borderline values for women were 451 to 500 ml per square meter and for men 530 to 550 ml. per square meter higher values were considered to be definitely pathologic. These values have proved to be reliable criteria in clinical practice[5] In the present paper relative heart volumes exceeding the ceiling limit and the borderline values have been referred to the group enlarged heart, and the smaller values to "normal-sized heart " The patients whose hearts had enlarged later are in the normal-sized heart" group to which they had originally been referred

The electrocardiograms were evaluated according to the criteria in general use[10] regardless of the findings of heart size in the patient concerned The findings were classified as transmural when definite pathologic Q deflections S-T segment displacement and T inversions were found at the height of the development of electrocardiographic changes, and as subepicardial or subendocardial when only S-T segment and T changes were seen respectively[10]

The limit of hypertension was set at 100 mm Hg or more of diastolic pressure at more than one recording[11,12]

Most of the surviving patients returned for follow up examinations about 2 months, 6 months, and 12 months after discharge from the hospital All those surviving were sent a questionnaire and invited for a later follow up examination 5 to 7 years after the first myocardial infarction. Out of 75 sixty nine patients actually came Five answered the questionnaire but did not arrive for examination. One patient with a normal-sized heart was known to be alive but he neither answered the questionnaire nor arrived for examination One patient in the group with enlarged hearts was known to be dead but particulars of this case were not available. In addition to the routine examination the patients were radiographed to determine their heart size

Results

The enlargement of the heart silhouette on x ray examination was mostly classified as general enlargement. In 10 patients it was predominantly left ventricular hypertrophy and 4 of these 10 had hypertension Left atrial enlargement associated with left and right ventricular enlargement was seen in 1 patient. "Left ventricular hypertrophy was also seen in 3 hypertensive subjects with normal relative heart volume and in 1 normotensive subject

In 49 of the 125 patients of the series (39 per cent) the heart was enlarged whereas for the other 76 a normal heart size was estimated at the first radiography *on recovery from acute infarction* Of these 76 with an initially normal heart size 32 per cent died within 5 years whereas of the 49 with an initially enlarged heart 53 per cent died within the same

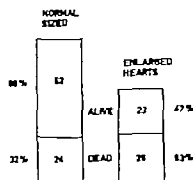


Fig. 1. Five-year survival in myocardial infarction *in patients with normal-sized hearts as compared* with patients whose hearts were enlarged when examined after the acute attack.

period (Fig. 1). The difference is significant ($p < 0.02$).

The better *survival percentage for the* patients whose hearts were initially of normal size is already visible after 3 and 6 months, and increasingly evident from year to year (Fig. 2).

Twenty patients with an initially normal heart size developed significant enlargement of heart volume later during the period of observation, and 6 of these 20 died. In 28 patients of the same group the heart size did not change and in 5 it diminished. Of these 33 patients, 2 died. A new measurement of heart size could not be performed in 21 cases. 16 patients died before the follow-up examination and 5 failed to appear for it.

In the group with enlarged hearts there were 10 patients whose relative heart volume increased further during the period of observation. 4 of these died. The heart size of 20 patients either did not change or decreased[1]. 4 of them died. Eighteen died before the follow-up examination, and 1 was unable to attend.

1. Influence of age. A review of the groups of patients (*Table I*) reveals that the mean age of the group with enlarged hearts is almost 10 years higher than that of the group with normal-sized hearts, and that the enlargement of heart and higher mortality rate are, especially among women, associated with more advanced age.

The percentage of patients with an *enlarged heart is shown by age group in* Table II, which also shows mortality of these age groups within 5 years. The lowest age group consists of 1 case only and thus provides no true illustration of the proportions. (We have, however, seen patients in this age group whose hearts at radiography immediately after acute myocardial infarction have been enlarged. Because of the shortness of the period of observation, however, these patients could not be included in the present series.)

In order to eliminate the influence of age, the series has been analyzed by age

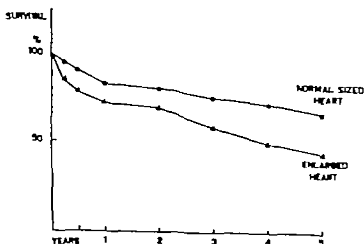


Fig. 2. Five-year survival in 125 cases of myocardial infarction.

Table I. Mean ages and age ranges of the patient groups with normal sized hearts and enlarged hearts

	Normal size		Enlarged	
	Alive	Dead	Alive	Dead
Men				
Number	45	22	16	16
Mean age	51	55	59	59
Range	36–67	42–80	46–73	46–75
Women				
Number	7	2	7	10
Mean age	60	56	61	72
Range	52–67	54–57	48–73	59–83
All	52.5		62.3	

Table II. Enlargement of heart and death rate in per cent of number of patients in different age groups

Age	Number of patients	Enlarged heart (per cent)	Dead (per cent in 5 years)
36	1	0	0
40–49	32	22	31
50–59	50	30	34
60–69	28	50	50
70–83	14	93	64

groups (Table III). Because of uneven distribution comparison is impossible within the lowest (under 40 years) and the highest (over 70 years) age groups. However, each of the three 10-year age groups in between shows a slightly higher mortality in the enlarged heart group. In the group of 60-69-year olds the difference is statistically significant ($p < 0.01$). For these three age groups combined (40-69 years) the difference just escapes ($t = 1.92$) statistical significance at a p level of 0.05.

2. Heart size and mortality. When the material is classified according to increasing heart size (Table VI), it is found that the mortality rate rises from the normal sized group to the borderline group and remains at the same level in the groups with a relative heart volume of up to 750 ml. per square meter; the patients with hearts larger than that have all died. The difference between the extreme groups is significant ($p < 0.001$) and if the three middle groups are combined, a significant difference ($p < 0.05$) is also obtained between the combined group and the two extremes.

3. Heart size and electrocardiographic changes. Electrocardiographic changes indicative of subepicardial or subendocardial infarction occurred relatively more frequently in the group with radiologically normal heart size than in the group with enlarged hearts; the mortality rate over 5 years was relatively highest in this latter group when electrocardiographic changes indicated a transmural infarct (Table IV).

For statistical analysis, to reduce the influence of age, the highest age group (of those over 69 years) was excluded. Furthermore, it was found (Table V) that an enlarged heart in combination with electrocardiographic changes indicative of transmural infarction increased the mortality rate significantly ($p < 0.05$) as compared with the other groups. During the follow-up examination no attention was paid to a possible shift to ventricular hypertrophy in the electrocardiogram.

4. Heart failure. As far as is known, none of the patients was in cardiac failure before entering this study. Of the 76 patients with hearts of normal size, 2 had congestive failure during the period of hospitalization for the first acute infarction (both of them died later); none developed heart failure during the first postinfarction year; 3 (1 died) developed failure 1 to 5 years, and 7 (no deaths) 6 to 7 years after the infarction.

Of the 49 patients with enlarged hearts, 6 had heart failure during the initial hospitalization (all 6 died later); another 2 developed failure during the first year (2 died), 6 (4 died) 1 to 5 years, and 7 (1 died) 6 to 7 years after their first myocardial infarction.

Altogether 21 patients (43 per cent) of this group and 12 (16 per cent) of the former group developed heart failure during the period of observation. Furthermore, there may have been patients who developed congestive failure (unknown to the authors) and before a follow-up study died at home.

Table III Death rate in different age groups of patients with normal sized and enlarged hearts

Age	Normal size			Enlarged heart			$P_2 - P_1$ ± S.D	
	Number of patients	Dead in 5 years	Per cent dead (P_1)	Number of patients	Dead in 5 years	Per cent dead (P_2)		
36	1	0	0	0				
40–49	25	7	28	7	3	43	15	22.2
50–59	35	11	31	15	6	40	9	15.4
60–69	14	5	36	14	9	64	28	10.1
70–83	1	1		13	8	62		

Table IV ECG changes and 5-year prognosis in patients with normal sized and enlarged hearts

Heart size	ECG changes			
	Subepicardial and subendocardial infarcts		Transmural infarcts	
	Number of cases	Per cent	Number of cases	Per cent
Normal	30	100	46	100
Alive	21	70	31	67
Enlarged	5	100	44	100
Alive	3	60	20	45

5 *Working capacity* Housewives, farmers, and manual workers accounted for 78 per cent of the group with normal-sized hearts and 49 per cent of the group with enlarged hearts, whereas the remainder was intellectual workers and the like

Of the patients surviving at the end of 5 years, roughly as many with an initially normal heart as with a heart size of borderline class were working whereas of those with heart sizes exceeding the borderline size, only 1 of the 13 surviving was working (Table VI)

Of the group with enlarged hearts, 21 were already incapacitated by age or illness, whereas only 5 of the group with normal-sized hearts were disabled (Table VII) Of this latter group one third of those working before their infarction were permanently disabled of the former 50 per cent could not return to work.

6 *Complicating diseases* Table VIII lists a number of diseases diagnosed in the patients in connection with the acute myocardial infarction or later The proportion of hypertensive patients (100 mm Hg or more of diastolic pressure) in the present series is relatively low 26 per cent of the total. The hearts of the hypertensive patients were enlarged as often as were those of other patients, and the mortality rate for the hypertensive patients in the 5-year period did not differ from the corresponding figure for the total series.

It was to be expected that the complicating diseases represented considerable additional strain In the group with normal sized hearts, 41 had complicating diseases and 29 per cent of these had died whereas 35 had no other diseases but 33 per cent of these had nonetheless, died In the group with enlarged hearts 29 had complicating diseases and 52 per cent of these had died whereas 20 had no other diseases and 45 per cent of these had died Thus additional diseases did not seem to have any appreciable effect on the mortality rate.

Discussion

The enlargement of the hearts of patients with coronary artery occlusion has been attributed by most authors either indirectly[2, 13-16] or directly[17, 18] to hypertension The coronary artery disease has been considered to be insignificant among the causative factors of enlargement of the heart,[14, 4] or the opinion has been that

*Table V. ECG changes and 5 year death rate in patients with normal sized and enlarged hearts**

Patient group	Number of cases	Number of deaths	Per cent dead	± S.D.
Normal-sized heart				
Subepicardial and subendocardial infarct	29	8	28	8.48
Transmural infarcts	46	15	31	6.73
Enlarged heart				
Subepicardial and subendocardial infarcts	4	1	25	25.0
Transmural infarct	32	17	53	8.93

*Patients over 69 years old were excluded.

Table VI. The relative heart volume, death rate, and working capacity 5 years after myocardial infarction

Heart volume (ml./sq. M.)	Number of patients	Dead		Living, not working		Living, working
		Number	Per cent	Symptoms	No symptoms	
Normal						
F 300-450 M 350-529	76	21	28	16	11	24
Borderline						
F 451-500 M 530-550	20	9	45	3	3	5
Enlarged						
F 501-600 M 551-600	13	6	46	4	2	1
601-750	11	5	45	5	1	0
751-1000	5	5	100	—	—	—

F, Female. M, Male.

Table VII. Working capacity before and after myocardial infarction

	Patients with	
	Normal sized heart	Enlarged heart
Not working before infarction	5	21
Working before infarction	71	28
Not able to work after infarction	24	14
Returned to work	46	13
Unknown	1	1

hypertension and coronary artery disease together[13,29] or hypertension and heart failure together[3,4] or heart failure alone[19] were responsible for enlargement of the heart.

Some authors are of the opinion that myocardial injury[20,27] myocardial infarction[20,27] or myocardial damage[24] may, without simultaneous hypertension, provoke dilatation and also hypertrophy of the heart muscle.

Among the numerous theories put forward to account for cardiac hypertrophy the first so-called injury theory was enunciated by Horvath[35] and later sup-

Table VIII Effect of other diseases on the 5-year mortality in patients with normal sized hearts and in patients with enlarged hearts

Patient group	All	Normal-sized hearts		Enlarged hearts	
		Total	Dead in 5 years	Total	Dead in 5 years
Total series	125	76	24	49	26
Hypertension	32	16	5	11	5
Pulmonary emphysema	13	10	2	3	1
Occlusive arteriosclerosis of the legs	14	10	3	4	2
Cerebral insult	7	3	2	4	2
Pneumonia	5	3	2	2	2
Cholecystopathy	7	3	0	4	4
Nephropathy	6	3	0	3	1
Tumors	5	3	1	2	2
Other severe disease	12	4	1	8	4

ported by the pathologic studies of Albrecht,[24] who stated that interference with the normal nutrition of the heart preceded hypertrophy.

Experimental and clinical observations led Eyster[22] to the conclusion that the most important factor contributing to cardiac dilatation and hypertrophy is the reaction to injury that results from abnormal stretching of the muscle in the initial period of overload as the lesion develops.

Subsequent clinical studies have adopted views which comply with earlier experimental findings. Master[19] points out that the aging process is an important cause of cardiac enlargement in coronary occlusion, and Amundsen[1] found that relative heart size grew with advancing age among the normal control subjects, patients with a coronary disease, and those with other heart diseases. In Amundsen's series, when elevated blood pressure and coronary disease acted together, the effect upon the relative volume of the heart seemed to be due chiefly to coronary disease. In the material reported on by Solem and associates,[17] the *incidence of heart failure* increased with advancing age after myocardial infarction. Problems concerning heart dilatation have lately been discussed by Harrison[24] in this JOURNAL.

In the present study an enlarged heart was verified radiologically in connection with the first acute myocardial infarction in 39 per cent of 125 patients. The mean age of the group of patients with radiologically enlarged relative heart size was almost 10 years higher, and their mortality rate within 5 years was *significantly higher* (53 per cent) than that of the group with normal heart size (32 per cent). In corresponding age groups, too, patients with an enlarged heart showed a higher mortality rate than those with normal-sized hearts. Therefore, it may be considered to be evident that if, when a patient is recovering from acute myocardial infarction, an enlargement of relative size heart compared with the normal or earlier size is noted, it means poorer prognosis *per vitam*. The higher death rate was also seen in patients who later during the follow-up period developed heart enlargement. Furthermore, as could be expected on the basis of common clinical experience, the patients with enlarged hearts developed *heart failure far more often* than did the patients with normal-sized hearts. Similarly, the working capacity of the patients with heart dilatation is poorer after recovery: one half of those who had been working prior to the acute myocardial infarction returned to work, whereas of the patients whose heart size was normal nearly two thirds returned to work.

The conclusion may be drawn, therefore, that enlarged relative heart size in connec

tion with myocardial infarction means a more severe pathologic process of the myocardium and coronary arteries. This accords with the results of earlier experimental[21,22,24,25,26] and clinicopathologic[4,5,11,20,23,24,27] investigations.

The same is suggested by the finding that transmural infarcts according to electrocardiographic changes, were more frequent among the patients whose relative heart size was larger than normal and these patients had the poorest prognosis.

The authors are of the opinion that radiologic measurement of heart size should be a routine examination for every patient recovering from an acute myocardial infarction. A heart size that exceeds the upper limit of normal is usually a sign of a severe myocardial lesion and myocardial weakness predicting a poorer prognosis. This should also be taken into account when the working capacity of these patients after recovery is evaluated.

Summary

In connection with the first acute myocardial infarction 39 per cent of 125 patients were found by radiographic methods, to have an enlarged relative heart size. The mean age of the group of patients with enlarged hearts was almost 10 years higher and their mortality rate within 5 years was significantly higher (53 per cent) than that of the group with normal sized hearts (32 per cent). The former group also contained a higher relative incidence of transmural electrocardiographic changes, the working capacity of its patients after convalescence was poorer and the incidence of heart failure was higher.

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Experimental and laboratory reports

A new system of multiple-lead exercise electrocardiography

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Despite the major importance of coronary artery disease (CAD) and the voluminous literature relating to it, its diagnosis prior to the development of serious complications remains notoriously difficult. To permit proper therapy a test is needed which can indicate a high probability of the presence of CAD. Coronary angiocardiography at present provides the most accurate information, but for obvious reasons it cannot be applied to large numbers of subjects, and this technique gives no information in regard to the physiological significance of an anatomic lesion. If myocardial ischemia can be detected accurately by a reasonably simple and safe test, and when demonstrated can be presumed to be produced by coronary insufficiency and in turn CAD, it may be used as an index to the presence of significant CAD.

Presently available electrocardiographic stress tests for myocardial ischemia give conflicting results in various hands. Recent summaries by Simonson[1] and Lepeschkin[2] permit us to avoid further review of the literature here. Suffice it to say that whereas some consider present tests to be very satisfactory, others using identical technique find them to be of almost no value.[3] We have initiated an investigation of the electrocardiographic stress test to determine whether parameters not previously investigated may increase the reliability of the results. There are, of course, many such parameters, but outstanding among them are adequate observation of the entire myocardial surface, use of multiple lead limb and precordial records throughout the period of stress as well as in the period of recovery, use of leads which are identical with standard electrode position leads so that stress records may be compared with the vast body of information on standard leads, and the provision of a means of stress appropriate for the state of disease and physical fitness of the subject.

We wish to report here methods we have developed for recording continuously or at frequent intervals multiple-lead electrocardiograms during as well as after exercise which are essentially identical with standard 12 lead electrocardiograms, and an exercise stress test flexible enough to provide appropriate stress to any subject.

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Fig 1 Leads 1 and 2 from standard electrode placement, showing the effect of finger motion on the base line

Lead placement system

Placement of the electrodes in the standard locations at the periphery of the limbs is of no value for the in-exercise ECG for the motion of even a single finger produces so much disturbance of the base line from muscle action potential that the record cannot be interpreted (Fig 1) Consequently we have explored the surface of the body to determine that placement for each of the limb electrodes (RA LA, LL) which would give records essentially free of muscle noise while the subject is walking climbing steps, or riding a bicycle ergometer and which would at the same time give records essentially identical in form and amplitude to records from standard placement position.

Fig 2 demonstrates the results of one

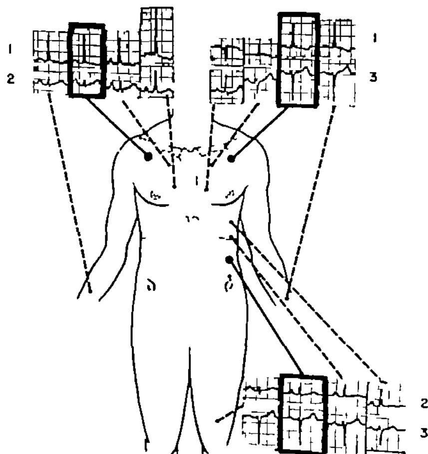


Fig 2. Diagram demonstrating similarity of limb-leads record from M-L points and standard peripheral electrode positions. Explanation in text.

such exploration. In this instance electrodes were positioned first in the standard peripheral sites. Then records were taken as the RA electrode was moved to progressively proximal positions up the right arm and over the upper anterior right chest. Since Leads 1 and 2 are those in which the RA electrode is used, these two leads are shown as derived from the positions indicated in the diagram. A position in the infraclavicular fossa medial to the border of the deltoid muscle and 2 cm. below the lower border of the clavicle was found to give records differing only to a very minor degree in amplitude from those of standard Leads 1 and 2, and to give a minimum of muscle noise during exercise of the types mentioned above. This point we label simply the "RA" point, indicated in the diagram by a black dot. Similar exploration was conducted to determine that the optimal position for the LA electrode is in the same relationship medial to the left deltoid and below the clavicle, and it is labeled by us the "LA" point. Leads 1 and 3 utilize the LA and are recorded as derived from the positions indicated in the diagram. Likewise the "LL" point was found to be in the anterior axillary line halfway between the costal margin and the crest of the ilium. Fig. 2 shows Leads 2 and 3 in the exploration with the LL electrode. This point is not so critical in location as the RA and LA points and can be varied a few centimeters in any direction to avoid skin folds, clothing, etc. Electrode positions for LL closer to the leg give no closer approximation of the R wave amplitude to that of standard LL position and they pick up too much muscle potential to be useful during exercise. Precordial electrodes are placed in the standard positions and when used along with the limb electrodes placed as outlined above and shown in Fig. 3 they permit the recording of up to 12 leads simultaneously or in any combination virtually identical with standard leads in form and amplitude except that simultaneous recording of multiple aV leads presents a problem of loss of amplitude which was recognized by King.[4] Where important this can be overcome by relatively simple electronic methods.[5]

We believe then that this placement

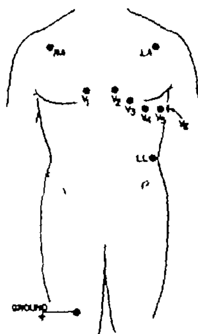


Fig. 3. Diagrammatic representation of placement of M-L limb and precordial electrodes.

system fulfills our requirement of giving leads that are essentially identical with those derived from standard peripheral electrode positions and yet obviates virtually all interference from muscle potential in the exercises used. It is referred to below simply as the M-L system.

In order to obtain a direct comparison between the M-L and the standard lead placement, 19 patients were studied as follows. Conventional 12 lead electrocardiograms were recorded with the patient in the supine position, using first the standard and then the M-L electrodes placed at the usual peripheral sites. A 12 lead record was then taken using the M-L electrodes placed in the positions shown in Fig. 3. A careful analysis was made on all the records of form, duration, and amplitude of P, QRS, and T waves. Since the amplitude of the P waves in all leads except Lead 2 and the amplitude of the T wave in Leads 1 and 3 were too low to be measured with the necessary degree of accuracy, these were excluded for purposes of comparison.

Qualitative scrutiny showed no significant difference in configuration of P, QRS, T, or the S-T segment between the standard and the M-L systems in any



Fig. 4 Photograph of subject with electrodes in place.

subject. The duration of the complexes was, likewise, identical in all the records from each subject. The results of the measurement of the ECG amplitude are shown in Table I.

The skin is prepared by rubbing it briskly at each electrode site with a gauze square moistened with acetone to remove oil and the most superficial horny layer thus lessening skin resistance. A semi liquid electrode paste has been found to be of ideal consistency for this electrode application. The LL electrode is placed so as to avoid creases in abdominal skin and the clothing is adjusted to avoid pressure on it. One or more strips of elastic adhesive tape† approximately 12 inches long should be applied to elevate the pectoral skin and breast, irrespective of

*ECG-Bel, Burton, Parsons & Co. Washington, D. C.
†Elastikon, Johnson & Johnson, New Brunswick, N. J.

Table I Comparison in mean amplitude of P RS and T M L expressed as percentage of standard ECG system

Lead	P(%)	R/S(%)	T(%)
I	—	79	91
II	123	122	125
III	—	140	—
V	—	104	103
V	—	99	106
V	—	107	116
V	—	100	100

Total number of patients, 19

Normal ECGs, 12. RBBB 1 LBBB, 1. LVH, 1 Myocardial infarct, 1 Ischemia, 1. Left axis deviation, 1

whether the subject is or is not obese. The importance of this simple maneuver is to keep the pectoral skin and subcutaneous tissue taut, thereby minimizing its motion during exercise, such as occurs particularly on landing during the 2-step exercise. This strap should be placed in position while the subject's left arm is elevated above his head before the application of the electrodes. The arm may subsequently be lowered to normal position. Precordial leads are placed so that the disc rides evenly between two ribs since there is less skin motion here than there would be if they were placed over lying a rib (Fig 4) The subject can be prepared for recording in 10 minutes by a well trained technician.

Electrode

To be interpreted accurately electrocardiograms must be free not only of muscle potential noise but of all other types of high frequency interference as well as base line drift. In developing our electrode design we have attempted to analyze the source of each of these types of interference with which the electrode is concerned, and have adapted the electrode to obviate the problem, as indicated below

A One of the most important causes of base line drift is gradual sliding of the electrode over the surface of the skin. The source of drift can be avoided by

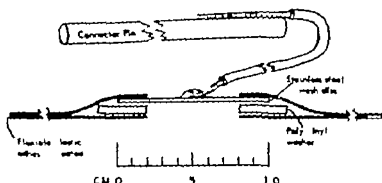


Fig. 5. Schematic diagram of electrode showing details of construction.

maintaining the position of the electrode constant in relation to the skin with some adhesive material. Low mass of the electrode in relation to the adhesive material and skin, and low torque because it is placed in close apposition parallel to the skin are mechanical factors of great importance in producing a stable base line in the ECG since they lessen motion of the electrode relative to the skin. Our electrode weighs only 0.5 Gm. and its plastic component in contact with the skin is adhesive so that it is tenaciously adherent.

B. Sudden or rapid shifts of base line are often due to intermittent contact of the electrode with the skin. We have found that the most satisfactory solution to this problem is the maintenance of a constant electrode-to-skin distance by the placement of a small nonconducting flexible plastic washer 0.5 mm. thick between the two in such fashion that there is no physical contact between the skin and the electrode. Electrical conduction is made then only via the electrode paste situated between the skin and the electrode (see Fig. 5).

C. Using permanent type electrodes of stainless steel, we have found evidence that with the passage of time and possibly because they have been worsened by surface scratches and chemical action of the electrode paste, the electrodes produce more and more interference, in that the slightest variation in electrode-to-skin distance creates a disturbing base line shift. This development has been avoided, how ever, by making our electrode disposable after one use and this type of interference has not been found during a 2 hour test period.

After investigating several other metals, we chose stainless steel as the material to use for the electrode because it has a low chemical reactivity with electrode paste, and it is relatively inexpensive, in contrast to the rare metals.

D. Mesh is found to work much better than sheet metal primarily because it permits excess paste to flow through and around it (the plastic being perforated to permit this), obviating the electrical problems developing when an air bubble is trapped between electrode and skin. The mesh size likewise is important. If the mesh is too large, records are of distinctly poorer quality, due possibly to inadequate surface area for signal pickup and to motion of the individual wires of the mesh. We have found that standard 100 × 100 mesh gives the best results.

The diagram of an electrode in section (Fig. 5) and the photograph (Fig. 6) of the top and bottom surfaces of the electrode show it to consist of a disc 1.0 cm. in diameter of 100 × 100 stainless steel mesh sandwiched between two layers of flexible plastic. The layer farthest from the skin has an adhesive coating only on its under surface, whereas that nearest the skin† is adhesive on both surfaces. A flexible polyvinyl washer 0.5 mm. thick and 1.2 cm. in diameter lies between the mesh and the skinward layer of plastic. The wire‡ is soldered to the mesh with

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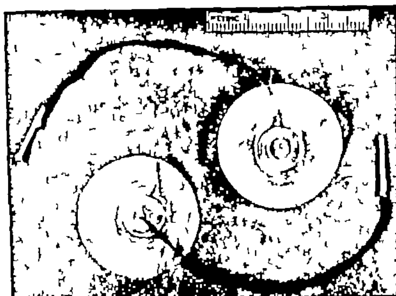


Fig. 6 Photograph of both surfaces of electrode.

stainless steel solder and flux. It, in turn is soldered to the male connector pin* which precisely fits the female connector† on the cable leading to the recorder The finished electrode is quite inexpensive, simple, and easy to make without elaborate equipment and is disposable.

Stress

It is axiomatic that any form of stress will produce myocardial ischemia if it is capable of producing inadequacy of blood flow in relation to myocardial need whether by a reduction in flow or an increase in need or by a combination of the two Four forms of stress are of potential use psychological pharmacological reduced oxygen content of the inspired air and external work. Psychological stress is too imprecise to be measurable thus far Pharmacological stress has not proved to be satisfactory because of complexity and variability of reaction, but holds promise for the future.

Tests making use of reduced oxygen in the inspired air have some advantages, but have never become popular In part, this is because they require special equipment and training of personnel However by their very design they are not of use in the large group of older patients who have cerebral arterial insufficiency since the brain is also very intolerant of ischemia. This may explain some of the reported adverse reactions to this test. Measurable external work, then appears to be the logical starting point.

The widely used two-step test of Master[6] has made a contribution to the assessment of general cardiovascular fitness, for which it was originally designed. As applied specifically to the detection of myocardial ischemia it has been of help when the results were strongly positive, but is far from the ideal solution. By Master's old criteria the results were too inaccurate.[7] Even with the use of recently developed criteria the accuracy is not adequate.[8,10] We agree with Scherf[9] that the concept of the application of a standard quantity of external work does not apply to the testing of an individual when one is interested in determining whether the subject develops ischemia under any circumstances, not just under a special set of circumstances. The prescribed set of exercises, whether single or double, does not appear to be standard for the purpose of demonstrating myocardial ischemia, for it produces too much work for some subjects in poor training and an inadequate amount of work for others more physically fit. This is a common observation and is

*Belden #8011.
†Electro Components test points EKT-1 Powell Co Philadelphia, Pa

objectively documented by the physiological studies of Ford and Hellerstein[9] and Simonson's group.[1] The test produces a varied heart rate that usually is far less than the maximum which is determined by age and not affected by training.[10] These and other considerations are summarized by Sheffield and Reeves.[11]

The in-exercise tests reported in recent years provide additional information on the physiological state of the myocardium during stress, with an increase in the percentage of positive tests by detecting ischemia which may disappear rapidly after termination of the exercise.[12] These tests, however, present records from an electrode placement system which is so different from the standard one that comparison with the base-line standard ECG is not possible,[12,13] and none to date has permitted in-exercise recording of limb leads.

Exercise carried out on a flight of stairs near the ECG station has been used by many. This falls short of our ideal criteria because the subject may develop pain or ischemic ECG changes at some distance from the bed, adding somewhat to the risk of the test. Furthermore, a cable long enough to permit in-exercise recording under these conditions is too cumbersome, whereas radio-ECG permits inadequate lead coverage, as mentioned above. One is left, then, with the use of some means of external work which can be carried out within a short distance of an ECG bed, and which can be performed by all subjects. There is no a priori reason to favor one means of external work over another, provided that the work is done close to the recording and resting area. One or two steps, the bicycle ergometer, and the treadmill all fulfill these criteria.

In our opinion, the Master steps are not ideal for providing heavier loads of work than those required in the 2-step test because of the speed of climbing necessary. For example, a 70-kilogram man must climb 60 steps per minute to perform 150 watts or 6,640 foot pounds of work, a level very easily adjusted on the dial of the bicycle ergometer at 40 to 50 cycles per minute. A single step, as used by Sheffield and Reeves[11] and others, is easier for the subject to manage at these rapid rates.

We have not used the standard treadmill since we have been concerned that its potential for frightening patients would introduce a significant element of psychological stress.

The Lanooy bicycle ergometer has been described elsewhere.[14] In essence, it is a stationary bicycle physically adjustable to the size of the patient. It makes use of an electromagnetic device whereby a given amount of work per minute is required of the subject over a fairly wide range of pedal turns per minute, with the amount of work being set by a rheostat dial that is adjusted by the operator. At the given range of work, in simplified version, the faster the subject pedals the less the resistance to the pedals at each revolution, and the slower he pedals the greater the resistance.

The test

Using the bicycle ergometer, we have started subjects at a level of work near or below that involved in the 2-step test, and have had them continue this work for 5 minutes, thus permitting the cardiovascular dynamics to reach a reasonably steady state of adaptation.[15] This period of work has been followed by a 5-minute period of rest to a steady state of cardiovascular dynamics again. Then another 5 minutes of work has been given at a *higher level of work*, followed by 5 minutes of rest. Graded increments of work have thus been alternated with rest until one of the following limits has been reached: (A) The patient complains of pain equivalent to that in one of his average attacks in daily life. (B) The patient complains of or is observed to show fatigue. (C) The heart rate reaches 90 per cent of the maximum predicted for his age.[10] (D) The monitored ECG during or after any level of exercise shows 1.0 mm. (or more) of ischemic S-T segment depression in one or more leads.

For "ischemic," we have chosen, on the basis of the observations of others,[16,17] the criterion of an S-T segment depressed 1.0 mm. or more and horizontal or down sloping for 0.08 second or longer. Electrocardiograms are recorded prior to exercise with the patients in the supine and erect position, in-exercise records being compared with the latter, and postexercise

supine records with the former Records are taken in-exercise at intervals no greater than every 30 seconds using Leads 1 2 3 aV_F V_3, V_4, V_5, V_6, since these have been observed to give the most information.

Discussion and results

Records taken by the system herein described have been generally of excellent quality even during quite strenuous exercise with considerable sweating and tachypnea. Some of the advantages of the system are illustrated by Fig 7 which shows a typical record at rest and during exercise at a heart rate of 188 Fig 8 shows a response with ischemic S-T segments as defined above, but with ischemic S-T segments developing in the limb leads only This might have been missed by other techniques. Ischemic change which occurs during exercise and which disappears almost immediately afterward is shown in Fig 9 In-exercise monitoring of records permits discontinuation of exercise when untoward changes develop in the ECG which obviously increases the subject's safety and comfort.

Using this technique, we have reported[19] the results of a study of 24 completely normal subjects compared with 30 subjects having classic Heberden's angina pectoris of effort. Each subject was given a double 2 step test and then after a rest period the graded exercise test described above. In only 1 normal subject was there a positive result. We anticipate that this percentage will be greater in a larger sample. Of the 30 subjects with CAD only 57 per cent showed ischemia, as defined above, by the double 2-step test, even given the advantage of multiple leads and in-exercise records. In 80 per cent the results were positive by the method described in this paper Thus, this technique gives a much better correlation with the clinical diagnosis than does a technique that requires less work of the subject. Analysis of results in a larger series is now being prepared in which comparison will be made with other methods

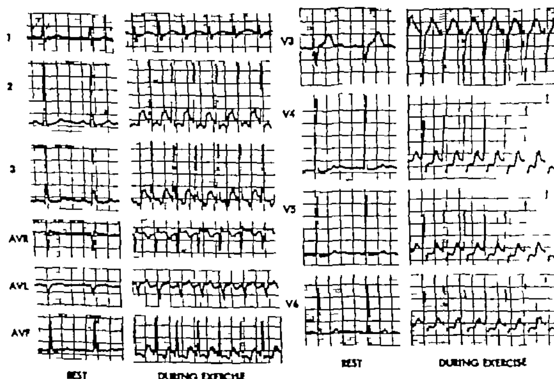


Fig 7 Electrocardiogram obtained during exercise, using the M L system. See text.

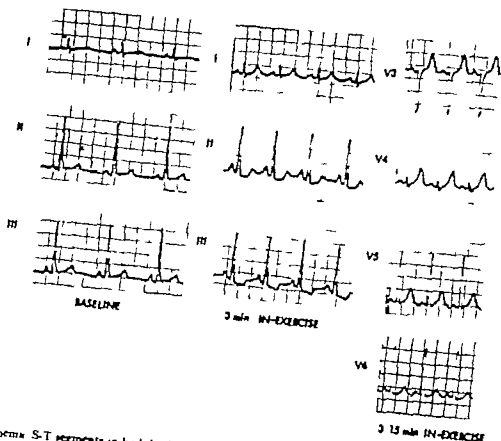


Fig. 8 Ischemic S-T segments in limb leads during exercise only. See text.

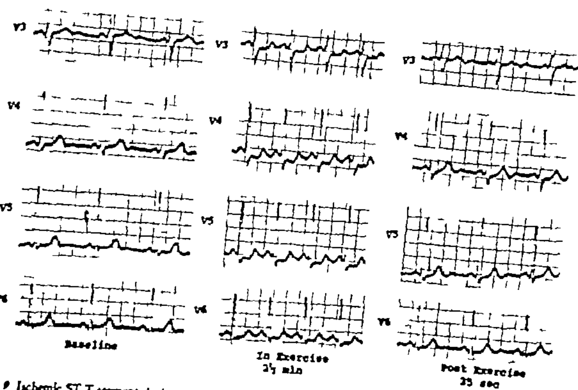


Fig. 9 Ischemic ST T segment during exercise only. See text.

of assessment of coronary disease, such as coronary arteriography.

Although there is value in obtaining stress electrocardiograms which can be compared to standard records, as mentioned above, there is no reason to assume that some other lead system may not be more sensitive for the detection of ischemia. This point remains to be explored. For the present, we believe that so much is to be gained from evaluating stress electrocardiograms by the criteria derived from standard records that the ability to record 12 lead standard-type electrocardiograms during stress represents a great advantage over nonstandard systems for the records of which there are no existing criteria for evaluation.

We clearly recognize that, although the criteria for ischemia listed above have been shown to have prognostic significance,[16,17] they are to some degree arbitrary. In subsequent publications we plan to assess the significance of these and other criteria more fully.

Summary

1. An electrode placement system is described which permits the recording of 12 lead electrocardiograms of excellent quality during exercise as well as at rest which closely resemble records derived from the standard peripheral position for limb lead electrodes. These records are essentially free of interference from muscle potential.

2. A light weight, disposable, inexpensive, stainless steel and plastic electrode has been developed which obviates virtually all sources of electrode interference, even during strenuous exercise.

3. A means is described whereby stress as external work in graded increments may be administered. Thus, work can be adapted to the state of disease and physical fitness of the individual at any level.

We wish to express our gratitude for the technical advice and assistance which we have received from Dr. S. A. Talbot, Dr. R. W. Sherwin, M. T. W. Winstead, and Mrs. Ilene Roberts.

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Central hemodynamics in recurrent embolism

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Obliterative pulmonary hypertension was considered by Wood[24] to be due to a restriction of the pulmonary vascular bed after obstruction of the pulmonary arteries by organic disease. The most frequent cause is recurrent embolism.

Knowledge of the central hemodynamics in this disease is, however, very limited and is based mainly on the data of Wilhelmsen[1] and Goodwin[11] and associates, who have studied a large number of patients.

Methods

Twenty patients with recurrent embolism were investigated. Twelve of them were referred for cardiopulmonary examination because of pulmonary hypertension of obscure etiology, and 8 patients were from our outpatient clinic. In the latter 8 recurrent embolism was suspected from the case history.

Diseases of the pulmonary parenchyma as well as congenital or acquired heart disease, were *ruled out in all subjects by* clinical examination, cardiac catheterization, and spirometry.

The venous circulation of the lower extremities was examined in all patients. In 15 dynamic phlebography of the lower extremities was carried out.[13] The case history was examined for clinical manifestations of embolism (paroxysmal dyspnea, hemoptysis, recurrent pneumonia, pleural pain) and for data on thrombophlebitis and venous thrombosis.

Painful, tender reddening of the skin above the veins without edema was evaluated as thrombophlebitis (inflammation of the superficial veins). Edema to the knee or the groin, associated with pain on walking or standing, and tenderness of the calf on palpation in the absence of inflammatory changes in the skin were evaluated as signs of inflammation of the deep veins.

A 12-lead electrocardiogram was recorded in all patients, and the lungs and the heart were examined by roentgenography. The latter evaluation was made on the basis of criteria presented elsewhere.[4] In all patients right heart catheterization was performed under local anesthesia. A polyethylene tube was introduced percutaneously into the brachial artery, or a *red Kifa catheter into the femoral artery.* Twelve of the patients performed exercise in the supine position on an Elema bicycle ergometer for 10 to 17 minutes. The load in most cases was 250 kilogram-meters per minute. The patients breathed through a mouthpiece into a Douglas bag for at least 3 minutes (between the fifth and

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eighth minutes of exercise) while samples of blood were drawn from the pulmonary and femoral arteries. The CO_2 and O_2 contents of the expired air were analyzed on a Zeiss interferometer the oxygen saturation on a Brinkman hemoreflectometer.* In 10 patients, arterial oxygen tension was measured by a Clark electrode and the arterial CO_2 tension, by the Astrup technique.[1]

In 8 patients the hemodynamic response to unilateral pulmonary artery occlusion was investigated.[24]

The effect of 10 minutes of inhalation of oxygen was examined in 7 patients.

In 2 patients, we investigated the effect of Priscoline (20 mg injected into the pulmonary artery) on central hemodynamics the method is described elsewhere.[20]

In 1 patient the influence of an infusion of acetylcholine on the lesser circulation was investigated. Acetylcholine was infused into the right atrium at a rate of 2 mg per minute.[23]

Results

The findings in the case records are summarized in Table I

In 6 patients the disease was preceded by the development of varicose veins phlebitis of the superficial veins was present in 14 patients. Seven patients had signs of thrombosis of the deep veins. As for the venous system of the lower extremities, only 3 patients (Nos. 5 14, and 15) had a negative history However all of these patients had a clinical history of embolization of the lesser circulation Paroxysmal dyspnea, which is the most frequent sign of embolization was found in 15 patients hemoptysis was reported in 11 patients. Recurrent "pneumonia was reported by 3 patients.

The results of objective investigation including phlebography of the veins of the lower extremities are presented in Table II Ten patients had edema of one lower extremity 7 had trophic changes, and 3 had crural ulcers. Six patients had parietal thrombi in the veins of the lower extremities 4 had evidence of obliteration of the deep veins.

*Kipp, Holland.

Central hemodynamics during rest (*Table III*) Mean pulmonary arterial pressure was increased (> 20 mm Hg) in 9 patients it was within the normal range in 10 patients. In 1 patient it was possible to insert the catheter only into the right ventricle, in which a normal pressure was recorded at rest. Whereas some patients (Nos. 10 and 20) had mild pulmonary hypertension in a number of patients the pressure in the lesser circulation approached that in the systemic circulation (Nos. 2 14 15 17 and 18) and in 2 patients it was almost equal to that in the systemic circulation.

Pulmonary capillary venous pressure was in no instance higher than 12 mm Hg In 2 patients it was not possible to obtain a satisfactory curve of pulmonary capillary venous pressure. The right atrial pressure in Patients No 2 and 19 was considerably elevated since both patients were investigated in right heart failure

The cardiac index was low In 3 patients it was less than 2 0 L./min /M² at rest, and in another 6 it was less than 2 5 L./min./M² In 9 patients, arterial oxygen saturation was normal (> 94 per cent) in 1 it was slightly reduced (90 to 94 per cent) 6 had moderate hypoxemia (85 to 90 per cent) and 4 had severe hypoxemia (< 85 per cent)

Central hemodynamics during exercise The pulmonary arterial pressure increased during exercise in all subjects examined on an average of 13 mm Hg ($p < 0.001$ $t = 6.182$) i.e by 71 per cent of the initial value ($p < 0.001$ $t = 4.729$) No correlation was found between the rise in pulmonary arterial pressure and the rise in cardiac output ($r = -0.109$) or the increase in oxygen consumption ($r = -0.477$) In 7 patients who had normal pulmonary arterial pressure at rest, pathologic pressures were recorded during exercise in 2 patients the pressure remained normal during exercise. In Patients No. 2 and 5 marked pulmonary hypertension was recorded at rest during exercise the pressure in the lesser circulation reached systemic levels.

Cardiac output rose during exercise on an average of 3.3 L. per minute ($p < 0.01$ $t = 3.990$) i.e., by 60 per cent of the initial value ($p < 0.01$ $t = 4.294$) The rise in

cardiac output was proportional to the increase in oxygen consumption ($r = 0.810$, $p < 0.02$). In Patient No. 5, who was examined in cardiac failure, a paradoxical drop in the cardiac output occurred during exercise.

The stroke volume increased by *16 ml* ($p < 0.025$, $t = 2.817$), i.e. by 29 per cent of the initial value ($p < 0.05$, $t = 2.489$). No significant correlation was found between the increase in the oxygen consumption and the increase in the stroke volume.

The pulse rate rose on an average of 22 beats per minute, i.e. by 25 per cent of the initial value.

During exercise, systemic pressure increased by 10 mm Hg ($p < 0.025$, $t = 3.079$).

Central hemodynamics during occlusion of pulmonary artery. Right or left unilateral pulmonary artery occlusion caused a rise in pulmonary arterial pressure in all 8 subjects examined (Table III). The rise was, on an average, 8 mm Hg ($p < 0.01$

Table I. Case histories of the patients studied

Patient number	Varicose veins	Phlebitis	Thrombus	Hemoptysis	Paroxysmal dyspnea et cet.	Recurrent pneumonia
1	−	+	+++	−	+++	−
2	−	±	−	+++	+++	−
3	−	+++	+	+++	+++	−
4	−	++	+	+++	++	+++
5	−	−	−	−	−	++
6	−	+++	−	−	+++	−
7	+	−	−	+	+	−
8	−	−	±	++	++	−
9	+	+++	+	+++	+++	−
10	+	+++	−	−	−	
11	−	+++	−	−	++	−
12	+	+++	−	+		−
13	+	+++	−	+++	+++	−
14	−	−	−	−	+++	−
15	−	−	−	+++	+	−
16	+	++	+	+++	++	−
17	−	+++	−	−	+	−
18	−	−	+	−	−	
19	−	+	−	+	++	−
20	−	+	−	−	−	++

+++ Three times or more

Table II Objective examination of veins of lower extremities

Patient number	*Varicose veins*	*Edema*	*Trophic changes*	*Ulcers*	*Phlebography*
1	±	±	–	–	Deep veins normal, insufficiency of communicating veins
2.	–	–	–	–	Parietal thrombi in fibular vein
3	–	+	+	–	Obliteration of deep veins of calf and thigh
4	–	+	–	–	Obliteration of deep veins of calf and thigh
5.	–	–	–	–	
6	+	+	–	–	Obliteration of deep veins of calf and thigh
7	+	–	–	–	Parietal thrombi in deep veins of middle and upper third of calf
8.	–	–	–	–	Parietal thrombosis of deep veins of calf
9	+	+	–	–	Deep eins normal, insufficiency of communicating veins
10.	+	+	+	–	Parietal thrombi in deep veins of calf insufficiency of communicating veins
11	–	–	–	–	Parietal thrombosis of deep veins of calf
12.	+	–	+	+	Deep veins normal, insufficiency of communicating veins
13	+	+	+	+	Obliteration of deep veins of calf and thigh
14	–	–	–	–	
15.	–	–	–	–	
16.	+	+	+	–	Incomplete obliteration of deep veins of calf and thigh, insufficiency of communicat ing veins
17	–	±	+	+	Parietal thrombosis of deep veins of calf and thigh, incomplete obliteration
18.	–	±	–	–	Deep veins normal, insufficiency of communicating veins
19	–	–	–	–	
20.	–	–	–	–	

Table III Central hemodynamics in patients with recurrent embolism

Patient	Age Sex	Condition of study	P_{PA} (mm Hg)			P_{PCV} (mm Hg)
			S	D	M	
1 A.D	27 F	Rest	17	6	10	4
		Exercise 250 kg M	21	7	16	—
2 F C	38 M	Rest	93	33	59	—
		Left PAO	113	39	69	12
		Exercise 100 kg M	128	49	85	—
		Rest + O_2	110	39	68	—
3 Z R.	31 F	Rest P_{RV}	27	3	—	—
		Exercise 250 kg M	44	8	—	—
4 J H	48 M	Rest	13	5	8	0
		Left PAO	16	9	13	0
		Exercise 250 kg M	29	17	24	0
5 A B	36, F	Rest	124	52	82	—
		Exercise 120 kg M	148	68	105	—
		Rest + O	136	55	84	—
6. A.K.	57 F	Rest	22	9	16	5
		Exercise 250 kg M	43	16	29	15
7 M J	48 F	Rest	24	12	18	—
		Right PAO	37	16	27	6
		Exercise, 250 kg M	42	16	31	14
8. A D	36, F	Rest	22	9	13	—
		Left PAO	37	11	27	5
		Exercise 250 kg M	37	16	26	8
9 K A	44 F	Rest	23	10	15	0
		Right PAO	28	8	17	6
		Exercise 250 kg M	—	—	17	7
10 J F	44 M	Rest	29	13	22	5
		Exercise 200 kg M	40	19	31	—
		Exercise 400 kg M	39	21	32	—
11 F J	50, M	Rest	24	10	16	10
		Exercise 250 kg M	34	15	24	17
		Exercise 500 kg M	45	13	25	—
12. R D	50, M	Rest	22	5	11	—
		Right PAO	34	8	21	5
		Exercise, 250 kg M	37	15	25	8
13 S K	43 M	Rest	27	8	17	9
		Rest + O_2	25	9	14	3
		Priscol	—	—	13	8
14 E H	54 F	Rest	84	42	56	2
		Rest + O	73	32	48	—
		Rest + Acetylcholine	77	41	53	—
15 B.S.	43 F	Rest	76	31	50	4
16. F.S.	53, M	Rest	26	13	17	—
		Right PAO	34	16	24	—
17 F D	31 M	Rest	74	32	48	12
		Priscol	—	—	51	—
18. A M	60, M	Rest	74	25	45	1
		Left PAO	95	29	55	0
		Rest + O	69	21	38	—
19 R.B	43 F	Rest	103	49	70	9
		Rest + O_2	—	—	—	—
20. A.K.	45 F	Rest	52	27	35	5
		Rest + O_2	—	—	—	—

P_{PA} Pulmonary arterial pressure. P_{PCV} Mean pulmonary capillary venous pressure. P_{BA} Brachial arterial pressure. P_{RA} Right atrial [illegible] (ml./min.) [illegible] Arteriovenous [illegible] difference. *H.R.* Heart rate. *S.V.* Stroke volume ([illegible] ml.). *C.I.* Cardiac index (L./ml. / [illegible]

P_{RV} (mm Hg)			P_{RA} (mm Hg)	$\dot{V}_{O_2}$	a-$\bar{v}O_2$	H.R.	S.V	C.I	Sa O_2
S	D	M							
138	94	111	—	220	5 9	84	44	2 5	96
186	91	127	2	623	—	120	—	—	93
116	84	95	14	324	7 7	90	47	1 9	89
127	93	105	—	382	8 9	90	48	1 9	89
142	107	125	—	558	10 6	108	49	2 3	84
120	87	98	—	—	8 8	90	—	—	99
117	72	92	—	257	4 3	78	77	2 9	96
117	62	85	—	660	7 5	102	87	4 4	97
109	68	84	−4	313	7 3	114	38	2 0	93
98	65	76	—	260	7 3	114	31	1 7	93
116	75	91	2	814	10 2	116	79	3 8	93
116	76	91	—	307	5 0	90	69	3 4	82
121	87	105	10	460	9 7	96	50	2 6	82
119	80	94	—	—	8 5	84	—	—	97
160	84	121	−1	260	5 3	72	69	2 5	94
175	91	121	6	873	8 7	90	112	5 0	96
166	108	134	—	197	3 4	96	61	3 6	89
157	100	134	—	218	3 2	96	71	4 2	91
152	117	137	—	622	5 8	132	82	6 7	92
118	75	95	0	226	3 2	96	74	3 8	95
—	—	—	—	193	3 6	96	56	2 9	95
150	97	115	4	725	5 6	132	98	7 0	97
175	83	128	—	311	5 1	66	92	3 1	96
150	83	108	—	280	5 1	60	92	2 8	97
159	94	122	4	695	—	90	—	—	100
121	64	86	—	331	5 6	96	62	3 3	96
121	75	98	—	785	8 0	120	82	5 5	95
142	77	100	—	1,051	5 0	120	94	6 2	93
117	68	87	—	308	6 2	72	70	2 4	99
129	79	98	—	675	8 9	90	85	3 7	95
141	86	104	—	1 080	11 2	102	95	4 7	97
119	61	83	2	315	4 0	90	88	3 9	97
120	61	86	1	—	4 5	90	—	—	99
139	73	98	4	831	8 2	108	94	5 0	100
110	90	97	−2	318	5 1	80	78	3 4	85
110	90	97	—	—	5 1	80	—	—	95
110	90	97	—	404	3 5	94	123	6 3	83
140	100	113	—	197	5 1	—	—	2 7	73
—	—	—	—	—	8 7	—	—	—	92
130	100	110	0	184	5 2	92	39	2 5	70
130	90	103	—	219	4 0	90	61	3 6	69
154	82	105	—	277	5 6	78	64	2 5	89
160	85	115	—	288	5 2	84	66	2 7	90
140	105	117	3	257	7 3	78	45	1 9	68
—	—	—	—	211	6 6	78	41	1 8	85
131	74	104	8	285	5 8	72	68	2 4	94
111	79	91	—	285	6 4	72	62	2 1	90
130	80	97	—	—	—	60	—	—	—
—	—	—	14	232	8 5	—	—	1 7	84
—	—	—	—	270	—	—	—	—	98
—	—	—	—	—	—	—	—	—	85
—	—	—	—	—	—	—	—	—	95

pressure P_{RV} Right ventricular pressure S Systolic pressure, D Diastolic pressure M Mean pressure, $\dot{V}_{O_2}$ Oxygen gas consumption [illegible], SaO_2 Arterial oxygen saturation (%) PAO Pulmonary artery occlusion.

Table IV Clinical and ECG diagnosis of pulmonary hypertension due to recurrent embolism

	Patient	ECG diagnosis of pulmonary hypertension	Clinical diagnosis of pulmonary hypertension	$\bar{P}_{PA}$ at rest	$\bar{P}_{PA}$ during exercise
1	A.D	0	+	10	16
2	E.Č	++	+	59	85
3.	Z.R.	0	0	27	44
4	J H.	0	0	8	24
5	V P	++	+	82	105
6.	A.K	0	0	16	29
7	M J	0	0	18	31
8.	A.D	0	0	15	26
9	K V	0	0	15	17
10.	J.F	0	+	16	24
11	F J	+	0	22	31
12.	R.D	+	0	11	25
13	S.K	0	0	17	—
14	E.H	++	+	56	—
15.	B.S.	++	+	50	—
16.	F.S.	0	0	17	—
17	F D	++	+	48	—
18	V.M	+	+	45	—
19	R.B	+	0	70	—
20	A.K.	+	+	35	—

ECG diagnosis of pulmonary hypertension positive (++) probable (+); negative (0)
The clinical diagnosis of pulmonary hypertension is the diagnosis made on the basis of physical examination.
$\bar{P}_{PA}$: Mean pulmonary arterial pressure, in millimeters of mercury

t = 7 117) In 6 patients the pulmonary arterial pressure at rest was normal and in 2 patients it remained normal even during occlusion During occlusion the cardiac output declined in 2 patients increased in 2 and did not change substantially in 2 The mean brachial arterial pressure declined in 3 patients in 2 it rose and in 2 it did not change substantially On the whole the change in pressure in the systemic circulation was insignificant. When the patients were evaluated individually it was found that during occlusion the cardiac output declined in 2 of them and rose in 2 and in 3 the change was smaller than 10 per cent

Response to inhalation of oxygen Inhalation of oxygen did not result in clear changes in pulmonary arterial pressure In 3 patients, mean pulmonary arterial pressure decreased (by 3 8 and 8 mm Hg) and in 2 patients it increased (by 2 and 9 mm Hg)

Response of pulmonary hypertension to drugs In 2 patients (Nos. 17 and 14) the effect of Priscoline or acetylcholine on pulmonary hypertension subsequent to recurrent embolization was investigated In both patients the pulmonary arterial pressure remained unaltered At the same time arterial oxygen saturation decreased in both patients.

Clinical findings All 9 patients with pulmonary hypertension at rest had abnormal electrocardiograms.[24] The diagnosis of pulmonary hypertension at rest is not difficult to make in patients with recurrent embolism Difficulties arise, however in the initial stage of recurrent embolism when pulmonary hypertension is present only during exercise As is apparent from Table IV pulmonary hypertension during exercise can be recognized by physical examination or ECG in only a small number of patients.

The hematocrit was higher than 50 per cent in 5 of a total of 16 patients. The correlation between the hematocrit and the degree of hypoxemia (Sa O_2 at rest) was at the border line of significance ($r = -0.545$ $p < 0.05$) In 10 of 19 patients the erythrocyte count was higher than 5 million but in only 2 was it higher than 6 million However the relationship between the erythrocyte count and the de-

gree of hypoxemia was significant ($r = -0.590$ $p < 0.01$)

Discussion

The symptoms of recurrent embolism depend on the site of the block. Obstruction of the trunk of the pulmonary artery or of the main pulmonary arteries can produce marked right heart failure (with suspicion of pulmonary artery stenosis) If the medium-sized branches of the pulmonary artery are affected repeated episodes of pulmonary infarction may occur with signs of progressive pulmonary hypertension leading to right heart failure. Obstruction of the distal part of the pulmonary arterial circulation need not be associated with signs of embolization, and the picture involves only signs of slowly progressing pulmonary hypertension This form may be very difficult to differentiate from primary pulmonary hypertension. A number of authors have repeatedly reported that patients with marked pulmonary hypertension may lack signs of embolization, despite a detailed analysis The diagnosis of primary pulmonary hypertension is usually made premortem but a large number of emboli in different stages of organization may be found post mortem.[2,4,10,13] Our experience, however indicates that detailed examination of the venous system of the lower extremities will detect pathologic changes in most of these patients. In 3 patients (Nos. 2 8 and 11) we found parietal thrombi despite a completely negative physical examination of the veins of the leg Goodwin and associates[11] describe two types of recurrent embolism Signs of the first type are found clinically in the case history of the patients, whereas the second type is manifest clinically only by increasing dyspnea. In our series of patients the latter type was found only rarely

Central hemodynamics in patients with recurrent embolism are varied. Normal findings in the lesser circulation at rest and during exercise were made occasionally in our group. In some patients even the elimination of one pulmonary artery from the circulation by occlusion did not lead to hypertension. A number of other patients who did not have pulmonary hypertension at rest did have more or less marked pulmonary hypertension during exercise Finally those patients who had marked pulmonary hypertension at rest showed a further increase during exercise. Some of these patients had pulmonary hypertension of a degree which is usually encountered only in patients with so-called primary or idiopathic pulmonary hypertension

No correlation was found between the number of emboli reported in the case history and the pulmonary arterial pressure This is well illustrated by Patient No 9 who despite twelve recorded embolic episodes had a normal pulmonary arterial pressure at rest, during occlusion and during exercise.

Pulmonary hypertension in patients with recurrent embolism responded poorly to oxygen inhalation Priscoline, or acetylcholine.

The source of pulmonary embolization in 95 per cent of the patients is thrombosis and thrombophlebitis of the veins of the lower extremities.[3,4] According to Mc Lachlin and Patterson[12] 70 per cent of the pulmonary emboli originate from the femoral veins. The pelvic veins and the right side of the heart are seldom the source of embolism[7] In our series, a history of thrombosis or thrombophlebitis, or parietal thrombosis in the veins of the lower extremities, apparent on phlebography was present. Thus, it is possible to consider the venous system of the lower extremities statistically and therapeutically to be the source of emboli in patients with repeated embolization It is essential to carry out phlebography in every patient, even when findings in the lower extremities are negative.

Our results indicate that most patients had manifest or latent pulmonary hypertension. These findings support our suspicion of recurrent pulmonary embolism A careful taking of the case history revealed clinical signs of previous embolization or of phlebitis of the lower extremities. Early diagnosis of recurrent embolism should be carried out in two ways first it is essential in patients with pulmonary hypertension of obscure origin to search for clinical signs of embolization and its possible source, and secondly after repeated inflammations of the veins it is

important to search for the initial stages of pulmonary hypertension

Conclusion

Twenty patients with recurrent embolism of the lungs were studied None of the patients had other disease of the pulmonary parenchyma or congenital or acquired heart disease which could be detected by clinical examination cardiac catheterization or spirometry Sixteen patients had signs of thrombophlebitis or thrombosis of the veins of the lower extremities. In all but 2 patients the data suggested embolization of the lesser circulation In most patients intravenous phlebography of the veins of the lower extremities demonstrated the source of the embolization Central hemodynamics were investigated in all patients at rest in 12 patients during exercise also and in 8 patients after occlusion of the pulmonary artery No correlation was found between the number of embolic episodes reported in the case history and the degree of hypertension in the lesser circulation Most patients had pulmonary hypertension of different degrees In the advanced stage the pulmonary arterial pressure was as high as the systemic pressure and pulmonary hypertension of this advanced degree was not influenced by the inhalation of oxygen or by acetylcholine or Priscoline

The clinical diagnosis of pulmonary hypertension was easily made in advanced cases of severe pulmonary hypertension however it was difficult to make in the initial stages of the disease when pulmonary hypertension was present only during exercise

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Atherosclerosis-inhibiting effect of an antibradykinin agent, pyridinolcarbamate

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The early stages of experimental atherosclerosis in rabbits have been characterized by an edematous arterial reaction that is not unlike the effect induced by excesses of bradykinin. Such experimental atherogenic techniques as serial injections of epinephrine and force feeding with cholesterol have all been characterized in the initial stages by an arterial edematous reaction. The main pathologic features of this reaction are accumulation of serous substances in the arterial wall resulting in transient enlargement of amorphous extracellular spaces, and adherence of platelets and leukocytes to the endothelial surface. German investigators have noted similar types of arterial change in early human atherosclerosis and have applied the descriptive term *das initiale fettfreie Ödem*.[1]

In a preliminary report in 1960, Shimamoto and co-workers[2] reported on the antiatherogenic effects of a weak bradykinin antagonist, nialamide. They demonstrated a significant preventive effect on the edematous arterial reaction and atherosclerosis in rabbits force fed with cholesterol.

Recently, a potent nontoxic bradykinin antagonist, pyridinolcarbamate (B_{31}), has been introduced in our laboratory, and its atherosclerosis-inhibiting effects have been studied in cholesterol-fed rabbits over a period of 2 years. A total of 118 rabbits was utilized, and the results of our findings are the subject of this report.

Materials and methods

Male albino rabbits weighing approximately 2.2 kilograms were selected for this study. The rabbits were a pure strain bred by the Takeda farm. All animals were kept in individual cages at a constant temperature of 21 ± 2°C. and constant humidity of 60 ± 5 per cent. After 1 month of observation, 118 healthy animals which showed a steady increase in body weight were selected for this study.

A 1 per cent cholesterol basal diet (RC 5) mixture was made into small pellets. Pyridinolcarbamate and a potato starch placebo were supplied in gelatin capsules.

The experimental study was divided into two parts. The first experiment was a 13-week study utilizing 72 rabbits. The animals were divided into six equal groups. The first group received a placebo capsule

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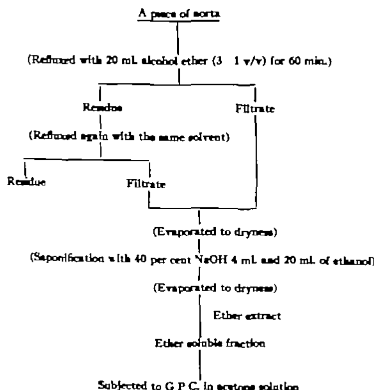
and the other five groups received pyridinolcarbamate in daily doses of 0.1, 1.0, 5.0, 10.0 and 50 mg per kilogram respectively. All six groups of rabbits were kept on 1 per cent cholesterol–basal diet pellets for 12 weeks. The daily consumption of pellets was limited to 120 grams. The amount of 1 per cent cholesterol–basal diet pellets consumed by each rabbit was recorded every day. The level of serum cholesterol was measured every other week by obtaining samples of blood from the central ear artery after 12 hours of fasting. The level of serum cholesterol was determined by the method of Zak[4] modified by Henley.[5] The rabbits were weighed every week. After 13 weeks, all rabbits were sacrificed for pathologic and chemical analysis.

The second experiment was a 15 week study utilizing 46 rabbits. All rabbits were kept on 1 per cent cholesterol–basal diet pellets, with a daily maximum of 150 grams. Twenty three of the animals received a potato starch placebo. The other 23 animals received a daily dose of pyridinolcarbamate (10 mg per kilogram). After 15 weeks of treatment, all animals were kept on basal diet pellets without cholesterol for 1 week prior to sacrifice.

Records of daily consumption, weight, and serum analysis for cholesterol similar to those of the first experimental study were obtained.

After completion of each experiment, all animals were sacrificed for pathologic study, including a quantitative measure of atheromatous lesions involving the aorta, and a quantitative estimation of cholesterol content of the aortic wall. For quantitative assessment of atheromatous involvement of the aorta a gross Sudan IV stain of the aorta was performed after fixation with Baker's solution. The aorta extending from the aortic valve to the origin of the

Table I. Extraction of cholesterol in aorta



left renal artery was carefully mapped utilizing transparent paper for the area involved by fatty streaks. The fatty streak portion was expressed as a per cent of the surface area of the aorta.

The cholesterol content of the entire aortic wall was determined by gas chromatography (Column: 1%, Chromosorb-w coated with SE-30. Detector: Hydrogen flame detector. Internal standard: Cholestane produced by Mass Research Laboratory.) The aorta extending from the aortic valve to the origin of the first intercostal artery was analyzed for cholesterol content after careful removal of the tissue adhering to the aortic adventitia. The aorta was weighed after the specimen had been dried at room temperature for 24 hours. Extraction of cholesterol from the aortic wall was performed as outlined in Table I.

Results

Experiment I. As shown in Fig. 1, the level of serum cholesterol exhibited a steady increase up to 1,500 mg. per deciliter for the first 8 to 10 weeks. There was no statistically significant difference in the levels of serum cholesterol among the six groups at the end of 12 weeks (see Table II). However, the percentage of surface involved by fatty streaks was strikingly different in the controls than in the animals which received pyridinolcarbamate (Table II, Fig. 2). The percentage of surface involved by fatty streaks in animals which received pyridinolcarbamate was small as compared with the placebo control group. Especially the group treated with 5 and 10 mg. per kilogram of pyridinolcarbamate exhibited the smallest percentage of surface involvement, and the striking differences of these two groups in comparison with the placebo control group is statistically significant at a level of $p < 0.01$.

The cholesterol content of the aortic wall is graphically illustrated in Fig. 3. The animals treated with pyridinolcarbamate exhibited a smaller cholesterol content than that of the placebo control group.

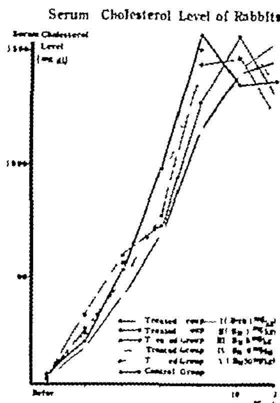


Fig. 1. See text.

Table II. Findings in control and pyridinolcarbamate B_{13}-treated group (mean ± standard

Group	Body weight (Kg.)		Daily food consumption (Gm./day)	
	Before	*12th wk.*	*1st wk.*	*12th wk.*
Control	2.36 ± 0.11	3.01 ± 0.13	108.5 ± 5.8	91.0 ± 9.9
B_{13} (0.1 mg./Kg.)	2.62 ± 0.07	3.04 ± 0.10	113.9 ± 3.0	95.1 + 6.8
B_{13} (1 mg./Kg.)	2.75 ± 0.05	3.01 ± 0.12	114.5 ± 3.2	10[illegible].0 ± 4.5
B_{13} (5 mg./Kg.)	2.64 ± 0.08	3.01 ± 0.11	113.7 ± 4.0	102.[illegible] ± 4.6
B_{13} (10 mg./Kg.)	[illegible]67 ± 0.08	2.99 ± 0.11	113.8 ± 3.9	86.4 ± 12.7
B (50 mg./Kg.)	2.65 ± 0.09	2.94 ± 0.11	117.0 ± 5.8	94.5 ± 10.3

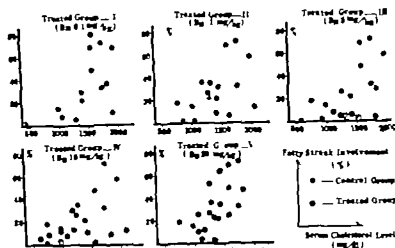


Fig 2 See text.

The smallest cholesterol content was found in groups treated with 5 and 10 mg per kilogram of the drug and the difference between these values and that of the placebo control group is statistically significant at a level of $p < 0.01$ (see Table III) A correlation was shown between the percentage of surface involved by fatty streaks and the mean serum cholesterol level in the placebo control group and in the group which received 0 1 mg per kilogram of the drug as shown in Fig 2 However in the other groups which received larger doses of the drug no correlation was found between the percentage of surface involved by fatty streaks and the mean serum cholesterol The results suggest that the administration of pyridinol carbamate in a dose of 1 0 5 0 10 0 and

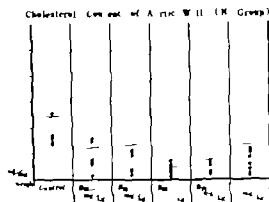


Fig 3 See text.

error)

Serum cholesterol level (mg /dl)		Fatty streak involvement (%)	Cholesterol content of aorta (µg/mg)
Before	12th wk		
35 2 ± 6 7	1 329 3 ± 161 3	39 9 ± 6 4	23 5 ± 4 4
32 6 ± 2 1	1 276 6 ± 207 0	27 9 ± 4 8	12 3 ± 4 6
44 0 ± 8 5	1 142 0 ± 100 5	26 5 ± 8 7	13 3 ± 3 8
24 7 ± 3 4	1 374 4 ± 219 4	9 3 ± 3 2	4 5 ± 0 8
27 2 ± 2 6	1 178 8 ± 145 0	11 9 ± 3 4	7 7 ± 1 3
43 2 ± 5 5	1 359 5 ± 120 3	26 3 ± 6 4	13 6 ± 4 4

Table III Cholesterol content of aortic wall (N—group)

Control group		Treated group									
		B_{12} (0 1 mg Kg)		B_{12} (1 mg /Kg)		B_{12} (5 mg Kg)		B_{12} (10 mg /Kg)		B_{12} (30 mg./Kg)	
Rabbit	Cholesterol	Rabbit	Cholesterol	Rabbit	Cholesterol	Rabbit	Cholesterol	Rabbit	Cholesterol	Rabbit	Cholesterol
N-69	10 3	N-4	1 2	N 24	1 9	N-27	1 0	N-44	2 0	N 38	1 5
65	13 5	3	6 2	21	3 3	35	1 6	46	2 7	49	2 4
63	14 3	7	6 3	20	3 6	28	2 5	47	3 3	59	3 9
71	16 1	10	6 5	15	6 2	31	2 8	42	5 4	36	5 5
68	17 1	9	6 6	14	9 4	33	3 2	48	6 2	52	8 5
0	19 0	12	14 0	19	10 4	30	3 5	43	6 3	50	10 2
67	25 5	2	15 4	18	11 1	36	4 2	37	7 7	54	10 5
66	36 2	1	42 2	16	19 9	26	5 3	40	9 2	53	10 8
64	42 1			13	28 9	29	7 1	45	9 2	51	20 0
62	50 8			17	38 2	32	9 3	41	9 6	60	24 7
								39	14 1	57	52 0
								38	16 3		
24 5 ± 4 4		12 3 ± 4 6		13 3 ± 3 8		4 5 ± 0 8		7 7 ± 1 3		13 6 ± 4 4	

*Micrograms per milligram of dry weight

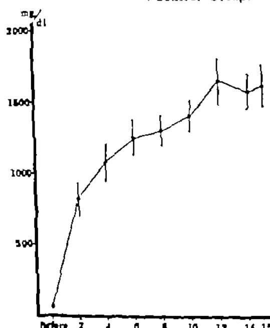
Table IV Findings in control and B_{12}-treated group (mean ± standard error)

	Control group	Treated group
Body weight (Kg)		
Before	2 75 ± 0 28	2 80 ± 0 26
15th wk.	3 39 ± 0 19	3 26 ± 0 20
Daily food consumption (Gm day)		
1st wk	135 3 ± 12 9	137 2 ± 13 6
15th wk	126 7 ± 6 7	120 4 ± 6 5
Serum cholesterol level (mg dl)		
Before	65 0 ± 10 8	73 5 ± 13 9
15th wk.	1 592 1 ± 147 1	1 735 3 ± 169 8
Fatty streak involvement (%)	63 2 ± 24 3	22 6 ± 13 2
Cholesterol content of aortic wall (μg/mg dry weight)	48 4 ± 9 3	9 3 ± 1 3

50 0 mg per kilogram prevented the appearance of fatty streaks

As shown in Table III and Figs 2 and 3 the animals treated with 5 to 10 mg per kilogram of the drug exhibited minimal atheromatous lesions and a very low content of cholesterol in the aortic wall despite extremely high levels of serum cholesterol which exceeded 1,500 or 2 000 mg per deciliter in some animals.

Experiment 2 Table IV shows the effects of pyridinolcarbamate and of placebo on the body weight and the food consumption of the animals The body weight of all



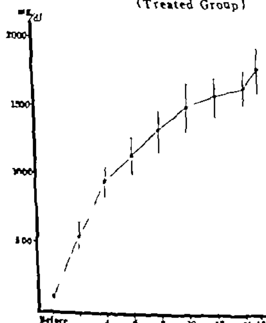


Fig 4 See text.

of the animals of both groups exhibited a slow increase. From these data, it seems that the body weight and food consumption of the rabbits did not change significantly on an atherogenic diet when the animals were treated with 10 mg of pyridinolcarbamate as compared with the controls receiving placebo on an atherogenic diet.

Fig 4 shows the levels of serum cholesterol in animals of the placebo control group and of the pyridinolcarbamate-treated group measured every other week throughout the whole period of 15 weeks. There was no statistically significant difference in the level of serum cholesterol between the control and the pyridinolcarbamate-treated group

Figs. 5 6 and 7 illustrate the striking preventive effect of pyridinolcarbamate on the formation of fatty streaks in the aorta and also on the accumulation of cholesterol in the aortic wall This was evident when the aortas for the drug treated and control groups were compared The slight difference in the consumption of food found between the control and the treated groups was also not sufficient to account for the protective effect of the compound

To facilitate a comparison of the results with the drug and placebo the data are presented in Figs. 5 and 6 and Table V which show clearly the striking preventive effect of the compound on the formation of fatty streaks and the deposition of cholesterol in the aortic wall even in the animals with an extremely high level of serum cholesterol exceeding 2,000 mg per deciliter for the prior 5 weeks.

Histological observation. There was a striking difference in the histologic characteristics of the atheromatous lesions between the placebo control group and the pyridinolcarbamate-treated group. A typical atheroma was found in the placebo control group with an accumulation of a large number of foam cells, accompanied by fatty degeneration and necrosis in its central portion In addition, a marked fragmentation of elastic fibers and the vacuolization of muscular cells were often encountered in the medial layers, as shown in Figs. 8*A* and 8*B* In the pyridinolcarbamate-treated group the atheromatous lesions were characterized by an appearance

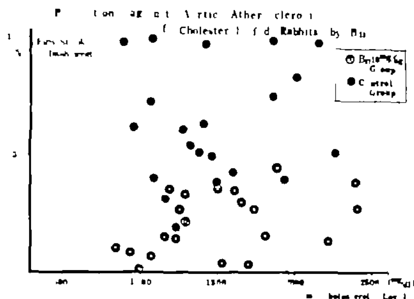


Fig 5 See text

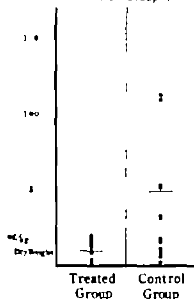


Fig 6 See text

of smooth muscles and elastic fibers in the intima accompanied by a few foam cells, and the internal elastic lamina was almost always well preserved. Fatty degeneration was rarely encountered and no necrotic portion was found as shown in Fig 8C. The atheromatous lesions show a tendency of fibrous healing characterized by a striking regeneration of smooth muscles.

Discussion

In the present series of experiments with rabbits kept on a cholesterol diet for 12 to 15 weeks, pyridinolcarbamate exhibited a potent antiatherogenic effect and a powerful preventive effect on the deposition of cholesterol in the arterial wall even in the animals with extremely high levels of serum cholesterol exceeding 2,000 mg per deciliter. The preventive effect of the compound does not appear to be dose dependent, i.e. 5 and 10 mg per kilogram per day appeared to be more effective in the prevention test than did a regimen of 50 mg per kilogram per day. No explanation for such evidence is available at the present time.

In the early stage of Shimamoto's investigation nialamide[8] was found to have a preventive effect on the edematous arterial reaction. Therefore nialamide was tested for its antiatherogenic effect in cholesterol fed rabbits and in the rabbits receiving repeated administration of Braun's dose[11] of epinephrine i.e. 1 μg per kilogram. A weak preventive effect[12,13] was found. Thereafter pyridinolcarbamate was found to be a potent bradykinin antagonist which was almost 10 times as effective as nialamide in preventing the edematous arterial reaction. This finding led to the present study in rabbits.

It is also noted that several antibrady

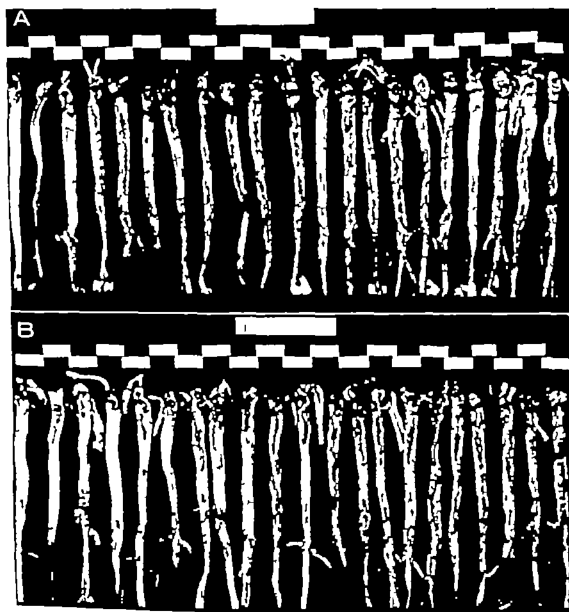


Fig. 7. The whole internal surface of aortas stained grossly with Sudan IV. *A*, From rabbits treated with placebo. *B*, From rabbits treated with pyridinolcarbamate. The percentage of surface stained by Sodan IV in the animals treated with pyridinolcarbamate (10 mg. per kilogram per day) is smaller than that in the animals treated with placebo.

kinin agents, such as reserpine,[6] guanethidine,[6] and cyproheptadine[6] have been shown by Schuler[16] and by the present authors[17] to exert an antiatherogenic effect. Needless to say, plasma kinins, such as bradykinin[3,4] and lysylbradykinin have been known to be potent factors which increase permeability in the blood and widen the endothelial gaps of leaking vessels[10,11] thus causing the leakage of serous substances, including substances of high molecular weight, such as enzymes, and formed elements into the tissue. Among the substances which appear by this means in the arterial wall from the vasa vasorum, some enzymes unfavorable to tissues of the arterial wall may exist, and these enzymes may digest and destroy local



Fig. 14. Transection of atheroma in the aortic wall of a rabbit in the control placebo group (hematoxylin-eosin). Note the typical atheroma with an accumulation of abundant foam cell accompanied by fatty degeneration and necrosis with cholesterol crystal.

structures of the arterial wall. The repetition of such phenomena may disturb the normal healing process by fibroblasts and fibrocytes and induce the accumulation of atheromatous substances fatty degeneration and the formation of necrosis as in the case of caseous lesions of untreated tuberculosis.

That pyridinolcarbamate acts to prevent the permeability-increasing and venoconstrictive effect of kinins in the vasa vasorum seems to be the key mechanism involved in the antiatherogenic effect of this compound.

Concerning the effect of endogenous inflammatory substances, such as bradykinin, Rowley[19] has shown the causative significance of their venoconstrictive effect by which the endothelial gaps in the venule are opened through an increase in the internal pressure of the blood vessels. On the other hand the direct influence of endogenous inflammatory substances on the endothelial cells was considered by Majno and Palade[7] and by Catran and Majno[11] to be another causative mechanism in the opening of endothelial gaps. Actually the occurrence of sticking of platelets and leukocytes induced by the administration of epinephrine or cholesterol has been found to be prevented by nialamide and by pyridinocarbamate and the sticking of platelets or leukocytes onto the endothelial cells may be considered to be an early stage of phagocytotic activity of endothelial cells. Harman[11] considered that

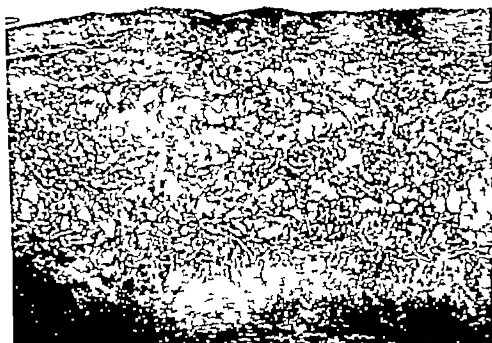


Fig 8B Same as Fig 8A



Fig 8C Transection of atheroma in the aortic wall of a rabbit in the group treated with 10 mg per kilogram per day of pyridinolcarbamate. Note that the atheroma is well organized by regenerated smooth muscles and fibrous materials.

the initial transport of lipid into the subendothelial space from the plasma, and its retention in the space, may be partly dependent on phagocytosis and/or pinocytosis. He tried an antihistaminic, chlorphenitamine in the prevention test of experimental atherosclerosis in cholesterol fed rabbits, because antihistaminics have been shown to inhibit the phagocytic activity of tissue macrophages, as well as that of injury activated endothelial cells and he found that chlorphenitamine had an antiatherogenic effect.

In the authors other experiment,[17] however the simultaneous administration of a potent antihistamine and antiserotonin agent, cyproheptadine and pyridinolcarbamate, failed to show any beneficial effect,

Table V. Cholesterol content of aortic wall and fatty streak involvement

Treated group			Control group		
Number of rabbits	Cholesterol content*	Fatty streak involvement†	Number of rabbits	Cholesterol content*	Fatty streak involvement†
F 19	0.3	1.4†	F 35	1.4	18.8†
F 4	0.4	15.0	F 44	5.2	31.4
F- 3	0.6	4.7	F 31	7.3	42.8
F-16	1.2	13.0	F 32	9.1	40.0
F-11	1.4	10.5	F-41	11.0	39.1
F 15	1.6	5.5	F 43	15.7	63.3
F 8	1.9	16.2	F 34	15.9	61.0
F 9	2.7	22.7	F-27	17.3	50.5
F 13	3.9	7.4	F 29	23.5	54.7
F 24	7.8	17.4	F 26	31.2	40.7
F 18	9.3	15.5	F 30	32.1	77.8
F 1	11.8	20.6	F 28	38.7	73.1
F 12	13.7	28.0	F-48	44.6	96.0
F 10	13.8	27.7	F-42	50.4	62.4
F 20	15.1	36.8	F-49	52.3	93.9
F 7	16.3	36.8	F 40	77.6	82.1
F 23	16.7	46.7	F 37	92.7	53.5
F 14	17.2	33.1	F 47	104.7	99.2
F 17	18.4	32.1	F 45	110.3	98.5
F 21	19.6	38.2	F 33	113.2	51.0
F 2	23.2	38.2	F 36	144.5	93.9
Mean ± S.E.	9.3 ± 1.3	22.6 ± 13.2	Mean ± S.E.	48.4 ± 9.3	63.2 ± 24.3

*Micrograms per milligram of dry weight.
†Per cent.

as compared with the effect of treatment with pyridinolcarbamate alone in the prevention of experimental atherosclerosis in cholesterol-fed rabbits, so that the antihistaminic activity per se of cyproheptadine as well as of chlorpheniramine seems not to be essential in the prevention of experimental atherosclerosis. Also, in still another of the authors' experiments[17] the atheromatous changes induced by the cholesterol feeding coupled with the intravenous injection of 1 μg per kilogram of epinephrine were also significantly prevented by the administration of pyridinolcarbamate in daily doses of 2.5 to 5 mg per kilogram. The effect of epinephrine activating the bradykinin-forming enzyme has been well known.[18]

Such evidences and the data obtained with nialamide[3] as well as the findings in the present experiment with pyridinolcarbamate, all suggest the importance of plasma kinins as a causative factor not only in the formation of edematous arterial reaction but also in atherogenesis, and stimulate further research on the role of antikinin substances as antiatherogenic agents which may effectively prevent not only the deposition of cholesterol under high levels of serum cholesterol but also the formation of atheroma, fatty degeneration, and necrosis of atheroma, and the formation of atherosclerotic ulcer which is the major cause of death in human beings today.

Summary

An antibradykinin and antikallikrein-bradykinin agent, pyridinolcarbamate (2,6-bis-hydroxymethylpyridine bis-N-methylcarbamate), has a potent preventive effect on the edematous arterial reaction and has been shown to possess an antiatherogenic property on the basis of the results obtained in the present series of experiments with 118 rabbits.

The feeding of a high-cholesterol diet to the animals over a prolonged period of 13 to 15 weeks was employed to induce the experimental atherosclerosis, and the daily administration of pyridinolcarbamate in doses of 5 and 10 mg. per kilogram was shown to exert a powerful effect in preventing the appearance of atheromatous changes ($p < 0.01$) and the deposition of cholesterol in the aortic wall ($p < 0.01$) even under extremely high levels of serum cholesterol exceeding 2,000 mg. per deciliter. It also prevented the formation of atheroma, its fatty degeneration and necrosis, showing a fibrous healing and a striking regeneration of smooth muscles in the lesions.

The antiatherogenic property of this compound is not related to an influence on the level of cholesterol in the blood; in fact, hypercholesterolemia is not depressed by the drug. The antiatherogenic property has been presumed to correlate possibly with the kinin-antagonistic effect of this compound.

Addendum

Since preparation of this paper, an additional series of 20 female rabbits have been subjected to treatment with pyridinolcarbamate for 15 weeks and have been sacrificed for analysis. The findings in this series are in agreement with those of the present report on male rabbits. That is, the amount of aortic surface involved by fatty streaks was 59.4 ± 11.0 per cent in all 10 animals of the placebo control group and 28.0 ± 8.3 per cent in all 10 animals of the group treated with 10 mg. per kilogram of pyridinolcarbamate ($p < 0.05$). The histologic findings were also essentially the same as those in the *male* rabbits.

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An experimental examination of factors responsible for the 'h' (d") wave of the jugular phlebogram in human beings

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Sir Thomas Lewis[1] has aptly commented on the value of the jugular phlebogram (JP): "There are no forms of irregular heart action which may not be identified by this method." In most descriptions of the classic jugular phlebogram, three positive waves are usually depicted; however, a fourth wave, the "h" wave, which was observed when diastole was long, has occasionally been described.[2-4]

Groedel,[5] in his monograph on the jugular phlebogram, found that attempts to explain the genesis of the "h" wave were confusing but noted that it occurred when ventricular filling slowed down. Thus clarification of this problem is required.

The factors responsible for the formation of the waves of the JP have been examined by three methods: first, by associating them with certain synchronous cardiovascular events;[7, 8] second, by experiments on animals;[7] and lastly, in human subjects by comparing the changes in volume in the jugular bulb with the changes in pressure recorded from a right atrial catheter.[9-11]

The purposes of this paper were twofold: first, to describe a series of experimental procedures which were used to elucidate the factors responsible for the formation of the "h" wave of the JP, and second, to further the examination of the events occurring during the diastolic filling phase of the cardiac cycle, a problem which merits greater examination.

Methods

The jugular phlebogram was recorded from the traditional site in the right supraclavicular fossa by a thin-walled rubber balloon 1 inch in diameter. The outer surface of the balloon had an indistensible plastic backing and was secured over the right jugular bulb with adhesive tape. This method allowed the subject to be tilted and to perform maneuvers, such as Valsalva's, without displacing the recording system. The balloon was inflated to a pressure of 3 to 5 cm. of water in order to fit the contours of the skin, and the pulsations were recorded through a Statham P23D transducer and a Grass polygraph. A similar balloon was placed higher in the neck over the left carotid artery. A stand-

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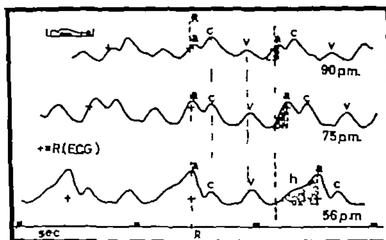


Fig. 1 The three records of the jugular phlebogram were obtained on the same occasion from the same subject during a period of rest. The tracings are aligned by the R wave of the ECG. The shaded area is that which is added to the cardiac cycle as the heart rate slows. It will be noted that the 'h' wave appears as the diastolic period is lengthened. The figures in this paper are reproductions of the original records, and it should be emphasized that in all these tracings a self-centering device was employed in order to avoid large drifts in the records.

ard electrocardiographic tracing was recorded from Lead II. As in a previous study[11] pressure cuffs were placed about the thighs and upper arms. The subject lay on a tilt table. The room temperature was 30 to 35°C.

An important part of the procedure was to train the subject to hold his breath in a standard relaxed fashion. He was asked to do this with his mouth and glottis open and with avoidance of respiratory straining. A control record was made from each subject for about 30 seconds to see whether any changes occurred in the JP when the breath was held.

The effect of the procedures used in these experiments is more readily seen when one makes a comparison of changes in successive waves. The change in the h wave is more obvious and dramatic when compared with its associated a, c and v waves (see Fig. 1).

Procedures and results

1. Relationship between heart rate and formation of h wave

A. VARIATION IN RESTING HEART RATE. Slowing of the heart rate will occur in normal subjects when they are allowed to rest in the recumbent position (see Fig. 1).

B. INDUCED CHANGES IN HEART RATE. An induced tachycardia followed by a sudden bradycardia was produced as follows. The veins of the limbs were drained by placing the subject in a head-down position (25 degrees) with the arms held in the upward vertical position. After a period of 30 seconds, venous-drainage suprasystolic pressures (200 mm. Hg) were applied to the four limb cuffs. The subject was then placed in a 5 to 10-degree head up position. After a period of 2 minutes of limb ischemia, the cuff pressures were released. This release caused a cardiac acceleration; when this tachycardia had fully developed in about 8 seconds, the high pressure in the cuffs was reapplied to the limbs. This caused a sudden bradycardia (see Fig. 2). As the heart rate slowed below approximately 60 beats per minute the h wave emerged to fill the lengthened diastolic gap (see Fig. 1). Again, where the heart rate was altered experimentally as described above, acceleration caused the disappearance of the h wave, but slowing promoted its return (see Fig. 2).

The possible explanation of this tachycardia and subsequent bradycardia, confirmed by indirect and direct recordings of blood pressure, may be as follows. The first release of suprasystolic pressure cuffs allows a sudden inrush of blood into the four limbs, simulating an arterial hemor-

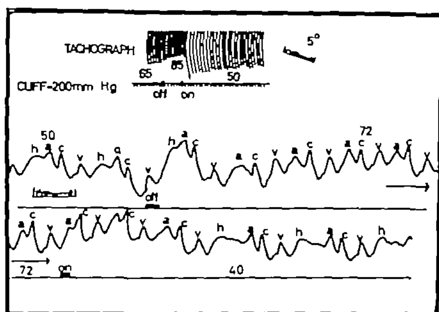


Fig. 2. The upper record is a tachograph. It shows the effect of the release and reapplication of pressure cuffs applied to the four limbs. (For details see text.) The numbers represent the heart rate in beats per minute. The tracing of the JP was obtained separately. The words *Off* and *On* represent the points of release and reapplication of the cuff pressures at 200 mm.Hg. It will be noted that with the induced tachycardia the h wave disappears, but reappears when the heart is slowed. The two lines of the lower record are continuous.

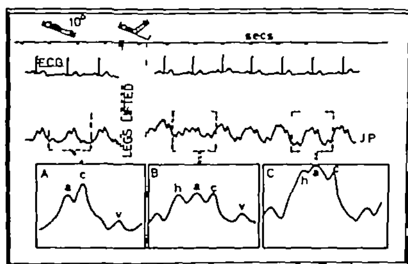


Fig. 3. This illustrates the effect of the passive raising of the legs; the JP recording during the leg-raising procedure has been omitted. In the frames in the lower half of the figure are enlarged selected wave complexes to illustrate the effect of the procedure.

rhage[11] and the drop in arterial pressure which ensues causes a reflex cardiac acceleration; the reapplication of the cuff pressures increases the resistance to the augmented cardiac activity and causes a sudden rise in arterial pressure and thus reflex bradycardia occurs.

2. Augmentation of venous component of jugular phlebogram

A. INCREASE IN VOLUME OF BLOOD IN CENTRAL VENOUS RESERVOIR. This was accomplished by passively raising the legs in a recumbent subject.

B. ACUTE TRANSFERENCE OF BLOOD FROM

LIMBS TOWARD HEART This was achieved by the release of venous congesting cuffs applied to the four limbs. The subject was placed in a 5-degree head-up position in order to obtain a short period of effect.

So that the effect of this acute filling of the neck vessels at different distances from the right atrium could be examined the subject was placed horizontally and the above mentioned procedure was repeated with a second recording balloon on the right or same side of the neck but situated more cranially than that over the jugular bulb in a position where carotid pulsations are recorded

C. INDUCED CENTRIPETAL VENOUS PULSATION A centripetal volume pulse from the peripheral veins may be artifically produced by the following procedure The subject was placed head-down at 15 degrees, and two sets of cuffs were placed upon the dependent arms. The distal set (on the forearm) was inflated approximately 1 second before the more proximal set (on the arms) the pressures applied to the cuffs were subdiastolic in order to avoid antidromic arterial pulsations.

Fig 3 shows that the passive lifting of the legs caused the production of an h wave. Since there was no slowing of the

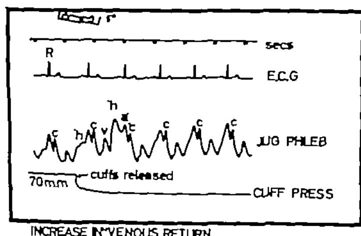


Fig. 4A This illustrates the effect of an increase in "venous return of short duration Note that there was no change in heart rate. The subject was placed 5 degrees head-up.

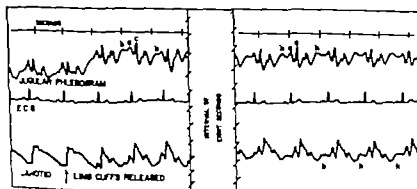


Fig 4B This is a repetition of the procedure of release of venous congestion cuff on the four limbs. The subject was horizontal, with the legs elevated 20 degrees The cuff pressures were 70 mm Hg and were applied for 2 minutes. The upper record is a jugular phlebogram the lower one is a carotid tracing made from a site bout 2 inches more cranially

heart rate during the appearance of the additional wave, this cannot be dependent upon bradycardia alone (see Fig. 3).

The main effect in this instance after the release of the venous congesting cuffs with the subject at 5 degrees head-up was an augmentation of the "h" wave (see Fig. 4A). This augmentation lasted for two cardiac cycles, whereas the other waves of the complex showed little change. No bradycardia developed.

When the two recording balloons placed at different distances from the right atrium were used with the subject horizontal, it will be observed (see Fig. 4B) that the release of the venous congesting cuffs caused first of all an augmentation of the "h" wave recorded from the lower balloon over the jugular bulb and this was followed by the appearance of the wave 13 seconds later at the recording point higher in the neck.

A series of centripetal venous volume pulses was made at different times in the cardiac cycle and it was found possible to augment in a selective manner the "h" wave. The suggestion that the procedure might cause a mechanical artifact is unlikely because when it was repeated with the subject's arms raised and the veins empty, the augmentation of the waves of the JP was absent or markedly reduced. The configuration of the JP is dependent not only upon positive tidal venous waves, but also upon negative waves when the veins tend to empty, so that this augmentation effect of a centripetal venous pulse of short duration from the peripheral veins will be more likely to summate with the central venous positive waves than with venous negative waves or waves of other origin. Thus, attempts to produce an augmentation of the "c" wave were the least successful. An increment of blood thrust into an "empty" vessel may be lost, but when it is added to a "full" vessel it will meet with a resistance and more readily produce a volume or pressure effect. The purpose of this approach was to promote a centripetal pressure and volume increment from the peripheral veins alone and to examine whether such a procedure would selectively augment the configuration of the "h" wave. Examination of Fig. 5 shows that this is possible.

3. Reduction in venous component in jugular phlebogram.

A. REDUCTION OF VOLUME IN CENTRAL VENOUS RESERVOIR. The most effective way of reducing the venous component without causing changes in the heart rate is to apply venous congestion to the limbs (Fig. 6).

B. INFLUENCE OF POSTURAL CHANGE. It is possible with the recording technique employed here to obtain satisfactory rec-

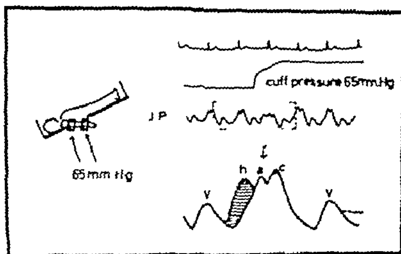


Fig. 5. This shows the effect of an induced centripetal pulsation. The shaded area in the enlarged tracing at the bottom of the figure shows the addition of the "h" wave.

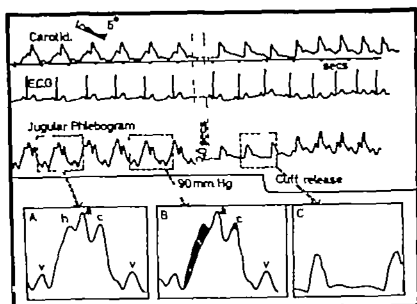


Fig. 6 This demonstrates the effects of venous congestion of the limbs. Frames *A* and *B* show in an enlarged form the results of this procedure on the 'h' wave. In this instance, the recording balloon was placed about ½ to 1 inch above the clavicle.

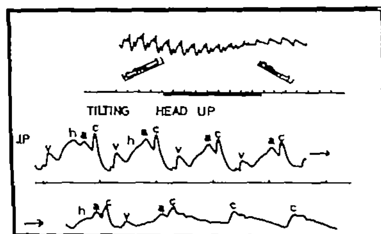


Fig. 7 The top tracing is a continuous tracing obtained during the process of tilting. The lower tracings were obtained on another occasion with greater amplification and a more rapid speed of record. The lower record more readily demonstrates the disappearance of the 'h' wave. The tilting was done from the head-down to the head-up position.

ords while the maneuver of postural change is in active process (Fig 7). In this instance the procedure was to tilt the subject into a head up position slowly and steadily. Such a procedure will reduce the pressure and volume in the veins in the region in which the JP is recorded.

C EFFECT AT SITE OF RECORDING OF AN INCREASE IN EXTERNAL PRESSURE. This is achieved by increasing the pressure in the recording balloon. This balloon is backed by indistensible nonslipping plastic material so that an increase in pressure inside the balloon will be transmitted to the underlying skin and cause a compression of the vessels. The vessels most likely to be affected will be those with a low internal pressure, the veins (see Fig 8).

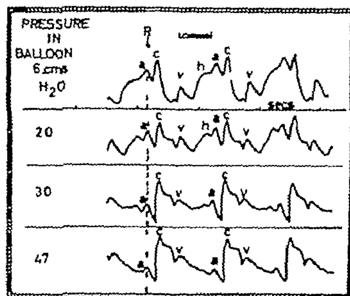


Fig. 8. These records of the JI were made at different balloon pressures. Note the absence of the "h" wave when the pressure reached 30 cm. of water.

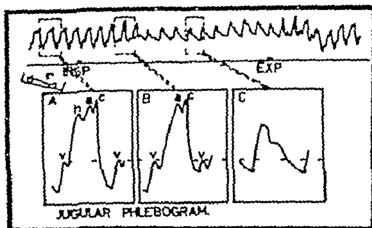


Fig. 9. This figure shows the effect of a continuous steady inspiration. The frames in the lower half of the figure show enlargement of individual waves.

B. EFFECTS OF INSPIRATION. Here the subject was instructed to make a steady slow inspiration over a period of 15 seconds. Inspiration will cause a negative pressure or "suction" effect in the veins in the supraclavicular region.

When venous congestion of the limbs was applied, the first element of the JI to disappear was the "h" wave and this occurred without changes in other waves of the complex. The heart rate increased slightly. Forty additional seconds were required in this instance to completely remove the remainder of the venous elements and to cause a matching of the carotid and JI pulse waves, which became characteristically arterial (see Fig. 6). When the subject was tilted head up, the disappearance of the "h" wave again occurred before the other waves were affected (see Fig. 7). This procedure caused some cardiac acceleration, which was not significant during the time that the "h" wave was disappearing. When the balloon pressure was raised, the "h" wave was the most readily obliterated. In this case it disap-

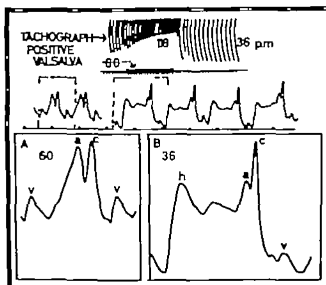


Fig 10 The upper tachograph was obtained during a positive Valsalva maneuver—when a column of mercury was blown up to 60 mm. The figures represent the heart rate in beats per minute The lower record was obtained on a separate occasion, and the parts of the record in which the heart rate was the same as in the tachograph were selected and enlarged. Under these circumstances there is a marked augmentation of the 'h' wave and the production of an additional wave which is at present innominate.

peared with a balloon pressure of 30 cm H_2O while the other waves were still present (see Fig 8)

In Fig 9 it will be seen that the h wave was *again the first* wave to disappear from the record soon after inspiration had begun

4 Combination of induced bradycardia and augmented venous pressure So far in these observations we have been attempting to demonstrate two things first, that the h wave can be affected by augmentation of the venous component of the JP and second, that it is rate dependent, that is, the length of diastole influences its formation. We thought, therefore, that it would be of interest to see what occurred when these two factors were combined This combined effect can be produced by a positive Valsalva maneuver Fig 10 shows the results of such a test. The upper record of the tachograph shows the dramatic effects on heart rate that such a procedure may produce Samples from a typical record are shown below The record in frame *A* was made prior to the Valsalva strain whereas that in frame *B* was made after the maneuver

5 Demonstration of venous origin of h wave from vascular pulsations in arm

A INDIRECT RECORD OF VENOUS PULSATIONS This was carried out as follows The subject was placed in a head-down position at approximately 20 degrees. The arm was supported in a 10-degree dependent position. A record such as that shown in Fig 11 may be obtained These pulsations are similar in character and in time intervals to those of the JP There is a delay in their relationship to the R wave of the electrocardiogram. Sometimes the waves are more confluent (see Fig 12) Some of the components of these waves are from the brachial arterial pulsations. This can be shown by applying a venous occluding cuff pressure proximal to the recording point, as in Fig 12 The resultant pulse wave was shown to be from the brachial artery since this latter wave was completely abolished by digital compression of the subclavian artery against the first rib

The above-mentioned procedures were carried out when an h wave was present in the arm pulsations Fig 12,*A* shows simultaneous records from the JP and the cubital region Before the second record was made (Fig 12,*B*) a pressure cuff

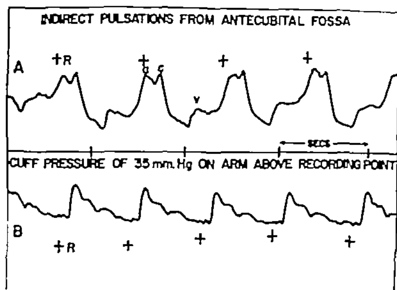


Fig. 11. This record was made from the surface of the antecubital region. It shows clearly the same waves and configuration as the classic jugular phlebogram. Note the conversion of this record into an arterial pulse tracing by the application of a cuff pressure proximal to the recording site.

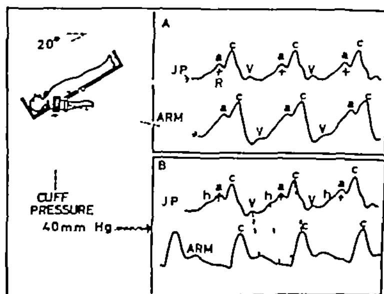


Fig. 12. The subject was placed 20 degrees head down. Two cuffs were placed on the arm. The proximal was a pressure cuff and the distal was a cuff containing the recording balloon. A shows a comparison of the arm and the JP records. B shows the effects of applying 40 mm. Hg of pressure to the proximal cuff. Note that a centering device was used in all of these records.

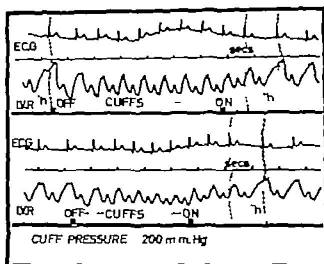


Fig. 13 These two records were obtained intermittently during a maneuver similar to that described in Fig. 2 when changes in heart rate were induced. Note the appearance of the 'h' wave when the pulse slows.

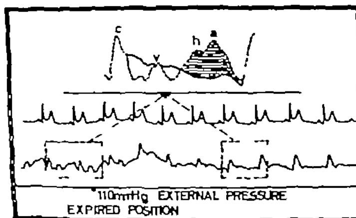


Fig. 14 The subject was horizontal. The breath was held in the expired position. Application of external pressure as described in the text caused the disappearance of the 'h' wave.

placed proximal to the recording balloon was inflated to 40 mm Hg in order to compress the veins and obliterate any central venous elements that might be reaching the recording point. Examination of the lower record shows that the 'h' wave was obliterated.

B. DIRECT RECORD OF INTRAVENOUS PULSATIONS These records were made through a needle in the median basilic vein. Cardiac acceleration was induced by the procedure described in Section 1B. It will be noted that the bradycardia was associated with the appearance of an 'h' wave in the record (see Fig. 13). That such a record came solely from the vein was demonstrated by the abolition of all pulsations when a pressure cuff at 25 mm Hg was applied to the arm proximal to the recording needle. Digital compression of the subclavian artery was without effect.

6. Influence of external pressures applied to chest. This procedure was devised because of the difficulty in obtaining satisfactory records of the JP during the Valsalva maneuver. Four large pressure cuffs were wound around the chest and abdomen and were covered by indistensible plastic strapping.

The application of the external pressure

to the chest is more likely to cause compression and collapse of the veins of the thorax than other vessels thus, the venous elements, including the h wave disappear from the JP leaving an arterial pulsation (Fig 14)

7 Examination of records of heart sounds Heart sounds were recorded from various sites on the chest wall by means of an N.E.P. suction microphone and a Honeywell Visicorder with a frequency response of 5 000 cycles per second Coincidentally records were obtained of the jugular phlebogram The outstanding feature of these records was the complete absence of any recorded sounds during that time when the h wave was formed up to the time of atrial systole Our procedures of positive Valsalva maneuver and increased venous return caused a marked amplification of the first second and what is significant the atrial component of the first heart sounds but no sound was recorded synchronously with the h wave

Discussion

Many factors have been described as being involved in the formation of the classic jugular phlebogram such as pulse waves from the right side of the heart arterial pulsations from the adjoining carotid artery and even the respiratory movements[7] Since the h wave occurs during ventricular diastole we concentrated on examining the cardiovascular events that occur during this period

From our results, the h wave appears to be of venous origin that is it occurs in the veins and emanates from the right side of the heart and is not due to any impulses transmitted from adjoining arteries thus it can be directly recorded from an intravenous needle in the median basilic vein In support of this suggestion is its disappearance when the veins are obstructed by a low pressure cuff applied proximal to the recording needle in the arm The similarity of intravenous records to those from a right atrial catheter has already been reported[11 11]

The indirect method of recording pulsations from the arm provides additional confirmation of the central venous origin of the h wave Here again when the subclavian artery is digitally compressed the residual venous pulsations are removed by a low pressure cuff applied above the recording site

Our results are in keeping with the suggestion that the h wave forms when the right heart is filled and when the filling or venous return is in excess of the output of the right heart as for instance when venous congesting cuffs on the limbs are released This was demonstrated when pulses were recorded from two sites in the neck one higher and more distant from the right atrium than the other When the venous congesting cuffs on the four limbs were released the h wave present in the JP tracing was augmented and a few seconds later an h wave appeared in the carotid record (see Fig *4B*) The anacrotic limb of the h wave in the record made closer to the heart was the steeper and its peak was closer to the preceding a wave Thus, this procedure caused the veins to the right atrium to become first of all overfilled and this filling process was extended a few seconds later upward into the neck veins.

The h wave was more susceptible to changes in central venous pressure than were other venous waves namely the a and v waves Thus it was the first to disappear when venous return was reduced by venous congestion of the limbs It was the first to disappear when the subject was tilted head up or when he inspired or when external pressure was applied to the recording site

In regard to the relationship of heart rate to formation of the h wave the diastolic period must be of sufficient length for the appearance and formation of the h wave The association between the appearance of an h wave and a slow pulse has been observed previously[3 4 8] and its appearance has been related to a long period of diastole[4] In our experiments when the pulse rate was below approximately 60 beats per minute the h wave appeared The peak occurred within 0 68 to 0 78 second of the peak of the preceding c wave This is in agreement with the measurements made on records presented in other papers[1 11]

The most dramatic change in the formation of the h wave was shown after the Valsalva maneuver which combined the

effects of bradycardia and venous engorgement.

We were unable to associate the formation of the h wave with any dynamic cardiac event. There was an absence of heart sounds during its production, even though procedures which produced or augmented an 'h' wave, such as the release of venous congestion caused an increase in the atrial component of the first heart sound.

The 'v' wave has been called "a venous stasis wave."[14] We would like to suggest that both the v and the h waves are formed by the same factors and are the result of a build up of volume in the great veins as the filling of the right side of the heart progresses in diastole. The reason that they appear as separate waves is the interposition of the negative ventricular filling y wave.

Summary

A series of experimental procedures was performed in order to elucidate the mechanisms involved in the formation of the h wave of the human jugular phlebogram. The conclusion was that this wave is a low pressure tidal wave of central venous origin and is related to the filling of the right side of the heart during diastole. The 'h' wave emerges only when the heart rate falls below approximately 60 beats per minute. No evidence from phonocardiographic studies could be found to associate it with any dynamic cardiac event.

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Dietary production of myocardial fibrosis in the rat

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A cardiac lesion has been produced in rats fed on a diet in which meal made from maize (*Zea mays*) is the prominent feature. The production of this lesion and its appearance, attempts at prevention by supplements, and some relevant biochemical assessments are described.

A pilot experiment was carried out in which different diets were given, copied from the type of diet taken by the local African population. These diets were varying combinations of the basic ingredients of maize meal, sucrose, sugar beans (*Phaseolus lunatus*), sour milk, and salt. Of 36 rats, only 7 survived more than 150 days, the remainder died from acute infections. The 7 survivors all showed cardiac lesions at death, which occurred between 431 and 495 days after placement on diet. The 4 diets which the survivors had taken were selected for an extended experiment.

Methods and materials

The 4 experimental diets are designated as Diets I-IV in Table I. Rats were allowed food ad libitum. Diet V consisted of standard laboratory rat pellets. The maize meal used was a standard unsifted meal, and the beans were those commonly consumed by the local African population as "sugar beans," *Phaseolus lunatus*. The sour milk was obtained from the whole milk of cows. The maize meal and beans were boiled in water, all ingredients of the diet were well mixed together, and the final food was in semisolid form. It was stored deepfrozen for periods of up to 1 week. The rats were allowed to breed and suckle their young. Fifteen female rats (Wistar), average weight of 160 grams, range 140 to 185 grams, and 10 male rats, average weight of 240 grams, range 190 to 280 grams, were allocated to each of the 5 diets. One year after placement on diets a group of rats from each diet was randomly selected to receive one supplement. The supplements were mixed into the food twice a week in doses as follows per rat: *dl* tryptophan, 175 mg., as a powder; nicotinamide, 1.17 mg.; pyridoxine, 35 μg. The timing of supplementation at 1 year after allocation to the basic diets was intended to provide a period of 3 months of treatment before the earliest lesion was to be expected.

In some cases, rats were found dead and occasionally their organs had been eaten. In other cases they appeared to be sick and were killed by exsanguination. A preformed plan was therefore difficult to follow exactly, but in so far as possible the planned killings were performed at 540 and 730 days after the diets were begun.

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Table I. Ingredients of diets (by weight as per cent)

Ingredients	Diet I	Diet II	Diet III	Diet IV
Cooked maize meal	49	48	36	36 5
Sucrose	5	4 5	3 5	3 5
Beans			32	32 5
Sour milk	46	46	27	27 5
Salt		1 5	1 5	

100 grams of cooked maize meal contained 60 grams of dry meal
100 grams of cooked beans contained 30 grams of dry beans (*Phaseolus vulgaris*)

and the experiment was terminated at 830 days. Exsanguination was performed in the early morning before renewal of the food supply for the day

Blood pressure was measured after intra peritoneal *pentobarbitone sodium* 45 5 mg per kilogram of body weight, by the tail-cuff method, using a binocular microscope to determine the moment of flushing of the tail during release of the cuff Measurements were made in duplicate and meaned to obtain the value accredited to an individual rat.

At exsanguination, blood was drawn into heparinized tubes for estimation of plasma tryptophan This was performed by a modification of Duggan and Udenfriend s method[1] in which the incident light was passed through a filter* with peak transmission at 296 mμ and fluorescence was measured at 360 mμ, in a Zeiss spectrophotofluorometer Experiments to recover *l*-tryptophan from plasma using this method showed 95 per cent recovery with added amounts up to 20 μg per milliliter Dietary tryptophan was estimated by Lombard and de Lange s method[2] The heart was removed and the ventricles were cut free from the atria. All blood was blotted off The ventricles were weighed and then fixed in buffered formalin, and processed by standard techniques to obtain sections stained by hematoxylin and eosin toluidine blue phosphotungstic acid-hematoxylin periodic acid-Schiff reagent, and Ponceau 2 R-light green Routine postmortem and microscopic examinations of other organs were carried out in addition. The severity of cardiac fibrosis was assessed 'blind through study of sections and expressed in arbitrary units from 0 to 4

Results

The results can be summarized as follows all experimental diets resulted in the appearance of the cardiac lesion after a minimum period of about 470 days, but the stock diet did not and no supplements prevented its development.

Rats which died before 170 days of diet have been excluded from consideration these and losses by cannibalism (6 instances) account for the discrepancy between the number placed on diets and the number of hearts assessed Causes of the early deaths were pneumonia, pyelitis and salpingitis.

Fibrosis

MACROSCOPICALLY *Affected hearts* were enlarged by dilation and by hypertrophy up to three times normal weight, the two ventricles being equally affected the atria occasionally contained adherent thrombi The left ventricular endocardium presented a range of appearances from normal to severely affected in such cases it had a whitish opacity and the trabeculae carneae had become fibrous cords, occasionally even locally calcified (Fig 1) In severe cases, some fibrous areas could be found in the wall The right ventricle was uncommonly changed in these ways, to the naked eye, and then to a slight degree only

Other findings at postmortem in affected cases were confined to changes secondary to heart failure, and occasionally to systemic embolism

MICROSCOPICALLY When present the endocardial lesion was a thin layer of fibrous tissue laid down on trabeculae carneae and papillary muscles (Figs. 2A and 3A) At the few calcified sites on trabeculae chondrogenesis had occurred below the fibrous tissue, and muscle was absent

The ventricular myocardium showed as the dominant features interstitial fibrosis and some edema hypertrophy of muscle fibers, and other changes in muscle cells. This fibrosis was present in a range

*Filter/UV obtained from Zeiss Switzerland



Fig. 1. Photograph of the interior of the left ventricle of a rat heart severely affected. The weight of the heart is two to three times greater than normal. The white endocardial opacity and some calcified trabeculae carneae are shown. (×4.)



Fig. 2A. The rat endocardial lesion is demonstrated. (×450.) (This and sections shown in all other illustrations were stained with Ponceau 2 R light green.)

severity from a thin diffuse network of collagen running between muscle fibers through a stage in which concentration of such fibrosis was locally more intense to the severe degree of patchy but complete scars seen by the naked eye at postmortem. These lesions are illustrated in Figs. 4A, 5A, and 6A. Figs. 2C-4C are comparable areas from hearts of rats fed the control stock diet (Diet A). In general, the fibrosis was more severe in the left than in the right ventricle and more severe in the inner one third than in the outer layers of the myocardium. There was often a tendency for the fibrous tissue to be spread around small arteries. Fig. 7 is a diagram of the characteristic sites of abnormal fibrosis. The fibrous tissue often showed *β-metachromasia*, but in some cases this was barely evident. The ventricular muscle



Fig. 2B The comparable human lesion. (X450.)

Fig. 2C. Normal rat ventricular endocardium. (X450.)

fibers themselves, besides hypertrophy showed other changes areas of cells and even individual cells would not take up the stains, or would do so imperfectly as can be seen in Fig 3A Yet their nuclei their cross striation, and their longitudinal fibrillar striation could be seen to be normal Such *nonstaining* cells were not stained by fuchsin according to Selye's technique[8] Sometimes a fiber in an area otherwise normal tailed off into wispy fibrous tissue suggesting its death and replacement by collagen.

A last change not uncommonly seen was an apparent diminution in the number of myofibrils in a cell especially easily seen in cross sections away from nuclei. With mitochondrial stains the sarcosomes can be seen stuffing the interfibrillar space.

Apart from congestive changes, microscopic study of other tissues showed only occasional and isolated abnormalities fatty infiltration of liver mild hepatic fibrosis, and cyst like dilatation of renal tubules. The tissues that were routinely examined included liver pancreas spleen stomach duodenum ileum and kidneys other tissues were examined when indicated by macro-



Fig. 3A. Rat left ventricular endocardium, showing fibrosis of the endocardium and between muscle fibers. The fibrosed trabeculae carneae and the appearance of the papillary muscle are typical of the lesion. (×63.)

Fig. 3B. The comparable human lesion. (×63.)

scopic examination. Striated muscle, bone marrow, and nervous system were sampled but not routinely studied.

Incidence of cardiac fibrosis in rats on the diets. There was no difference between dietary groups I-IV, either in totals or within subgroups by supplementation or sex; therefore they are considered together. Forty-nine of 72 rats had cardiac fibrosis, 30 of 43 males and 19 of 29 females. Fibrosis was present in 18 of 32 rats receiving no supplement, in 15 of 20 given tryptophan as the supplement, in 6 of 9 given nicotinamide, and 10 of 11 given pyridoxine. In 15 rats on Diet V there was no fibrosis in 10 males and 5 females. This diet was, in any case, the standard diet of the laboratory's colony, in which this fibrosis has never been seen.

Of the 23 rats on Diets I-IV which failed to develop fibrosis, 13 died or had to be killed within 4[illegible]0 days of being placed on the diets and may not have had time to develop visible manifestations. However, 6 of the unaffected had been on the diets for as long as 830 days, 3 in groups receiv-



Fig. 3C. Normal rat trabeculae carneae. (X63.)

ing no supplement and 3 in groups given tryptophan or nicotinamide as supplements. In the group on the stock diet (V) 12 of the 15 were killed more than 470 days from the beginning and 8 more than 730 days from the onset.

The number of pregnancies correlated significantly with the severity of fibrosis in the 32 female rats surviving beyond 470 days on Diets I IV (r = 0.85 p < 05)

Ventricular weights The ratio of ventricular weight to body weight was significantly increased above control values in the unsupplemented groups I IV between which there were no differences. The stock diet value (N = 6) was 00324 ± 000483 (S E.) and for the experimental groups (N = 30) the mean was 00508 ± 000253 (p < 05)

Weight ratios in supplemented groups I IV were as follows tryptophan (N = 20) 00376 ± 00039 nicotinamide (N = 8) 00543 ± 000612 pyridoxine (N = 11) 00493 ± 000323 These means do not differ significantly from the unsupplemented value. Supplementation of Diet V similarly made no difference in the ratio as compared to the unsupplemented value.

That the 10 hearts of dietary groups I IV unaffected by fibrosis after 470 days on diet were not necessarily normal is shown by the fact that they were significantly heavier than the 17 comparable hearts of dietary group V Mean heart weight to body weight ratios were 00466 ± 00024 (S E) and 00340 ± 00026 respectively for which p < 01 The average lengths of time on diet were, respectively 754 and 726 days for the two groups.

An analysis was made of the effect of the duration of diet on heart weight to body weight ratio and the severity of fibrosis. Whether individual supplement groups, or diets, or sexes were separated out for assessment, the duration provided that it exceeded about 400 days, had no effect on the ratio and provided that it exceeded 470 days, had no effect on the severity of fibrosis

Within these limits, therefore, the duration of diet can be neglected In addition mean durations of the different diets and of supplementations were comparable except where otherwise stated compared groups were alike in this respect.

The effect on the heart weight to body weight ratio of the number of pregnancies was also assessed under the same conditions as for the severity of fibrosis. The correlation coefficient was 0 89 in the 32 cases for which p < 02 This correlation in the group on Diet V was not significant.

Tryptophan levels in diets and plasma The tryptophan contents of diets I IV were similar in all Tryptophan content ranged from 18 0 to 31 6 mg per 100 grams wet weight, mean value 27 1 mg per 100

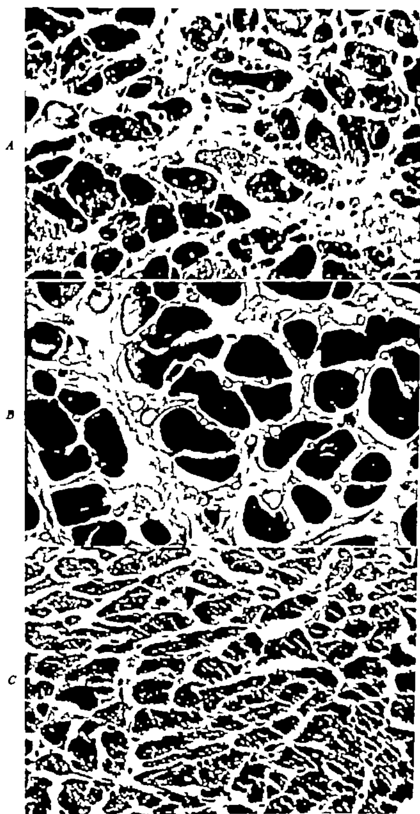


Fig. 4A. Fine intermyofiber fibrosis in the rat heart. (×450.)

Fig. 4B. The comparable human lesion. (×450.)

Fig. 4C. Normal rat myofibers and interstitium. (×450.)

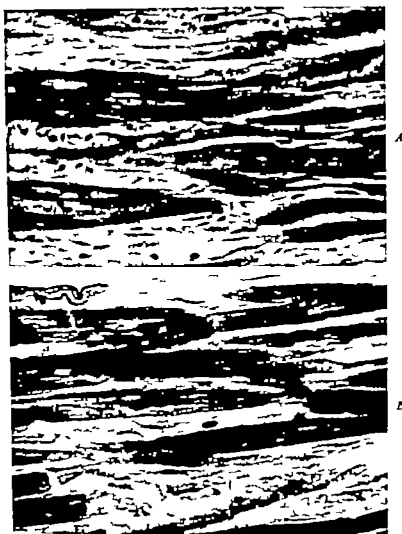


Fig. 5A The fine fibrosis seen between myofibers in longitudinal section rat heart. (×450.)
Fig. 5B The comparable human lesion. (×450)

grams. Moisture content decreased with deepfreeze preservation only by 3 per cent in 1 week from the initial 60 per cent of freshly prepared food. Measurement of the wet weight of the food of Diets I IV eaten when the rats were healthy and mature showed an intake of up to 30 grams per day equivalent to about 12 grams dry weight. The weight of Diet V eaten by adult rats daily averaged 22 grams for males and 16 grams for females, and this food contained 133 mg of tryptophan per 100 grams.

Plasma levels of tryptophan were as follows in micrograms per milliliter Diets I IV unsupplemented by tryptophan (N = 10) 17 6 ± 1.25 (S E.) supplemented by tryptophan (N = 6) 14.54 ± 2 78 Diet V unsupplemented by tryptophan (N = 6) 25 75 ± 3.5 supplemented by tryptophan (N = 4) 27 0 ± 2.86 Supplementation therefore, made no difference but Diets I IV were associated with levels significantly lower (p < 02) than those for Diet V whether supplemented or not.

Correlation between plasma levels of tryptophan and the severity of cardiac fibrosis shows an inverse relationship In the 16 available comparisons within Diets I IV the correlation coefficient was −0.59

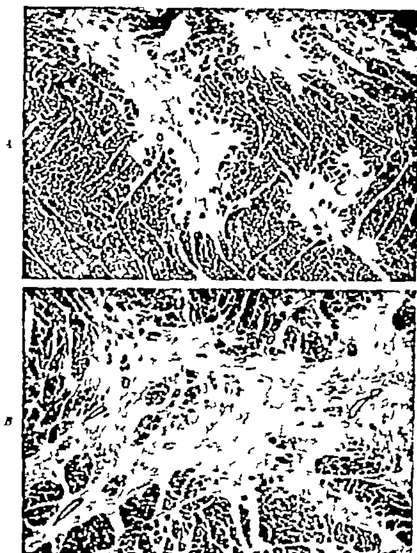


Fig. 6A Isolated microscopic scars, rat heart (X63.)

Fig. 6B The comparable human lesion (X63.)

for which p < .02 An analysis of sex differences all diets considered together shows means of 17.0 ± 1.71 (S.E.) µg/ml for females and 22.44 ± 2.26 µg/ml for males. This difference is significant only at a level p < .1

Blood pressure Arterial pressure was measured at 1 year after placement on diets, in samples of 5 males and 5 females from each dietary group There was no significant difference between any groups

Effect on pregnancy The association of pregnancy rate with various measurements has been mentioned In addition it is possible that the different diets and supplements had particular effects on the pregnancy rate and duration of productive life. Analysis showed no such particular effects to be present.

Discussion

The daily intake of tryptophan by adult rats on unsupplemented Diets I-IV can be estimated to have been at a maximum of about 9.5 mg., and for Diet V the mean figures are 29.3 mg for males and 21.3 mg for females. Daily requirements of adult rats on the present diet are not

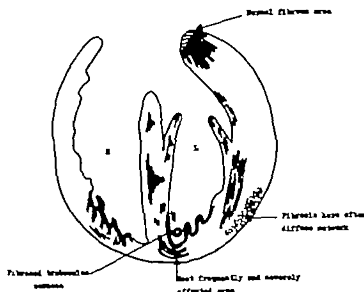


Fig 7 Diagram to show sites of predilection of the fibrosis in rat heart.

precisely known. Oesterling and Rose[4] found a minimum *l* tryptophan level of 0 15 gram per 100 grams dry weight of a synthetic diet necessary for normal growth over 4 weeks in weanling rats. A casein hydrolysate diet containing about 3 mg per day produced severe deficiency and early death[4] the addition of 01 per cent tryptophan equivalent to about 1.2 mg per day to a similar diet[4] failed to prevent widespread changes, but these rats survived far better The addition of .2 per cent tryptophan equivalent to 24 mg per day prevented deficiency [5,6] The range between adequacy and rapidly fatal inadequacy therefore, lies between 4 and 27 mg per day but, obviously age and other dietary features will affect the severity of any one level of intake of tryptophan. The rats on Diets I IV showed no lessening of growth nor of final weight compared with those on Diet V which closely resembled the published normal [7]

The plasma level of tryptophan in rats on Diets I IV reflect the dietary inadequacy Unexpectedly added *d-l* tryptophan had no effect on plasma levels. If there is any biologic significance in the inverse correlation between plasma tryptophan and the severity of cardiac fibrosis and enlargement, then the reason that tryptophan supplementation was not associated with an absence of fibrosis may be that there was a failure of absorption Alternatively supplementation may have come too late to prevent development of the visible fibrosis, and this would apply to other supplements as well The correlation may also be causally irrelevant.

The occurrence of cardiac lesions on a diet similar to the present diets has been reported before,[8] but not further investigated. The production of myocardial lesions on synthetic diets specifically deficient in tryptophan has also been reported [4,9-11] but the severe deficiency there reported was associated with acute lesions unlike those of the present picture

It would be extraordinary if this experimental cardiomyopathy did not bear resemblances to some of the described experimental cardiomyopathies, such is their profusion.[3] Elements of the whole picture are undoubtedly the same as have been described in human beriberi[12] and experimental thiamine deficiency [13] Nevertheless, the whole picture, and particularly the general appearance of slow fibrosis differ significantly from these other experimental cardiomyopathies. Of natural diseases of the myocardium the cardiomyopathy of Africans who live extensively on maize resembles this experimental lesion the most closely [14,15] Corresponding ap-

pearances in this human lesion are shown in Figs. *2B-6B* and Fig. *7* would do equally well for the human lesion. The experiments would also fall in with possible explanations of other findings: the cardiomyopathy of alcoholics, who have low blood levels of tryptophan[16] and abnormality of 5-hydroxytryptamine metabolism[17] and the association of cardiac failure, especially that of African cardiomyopathy, with pregnancy and the postpartum,[15,18] in which case not only is maternal tryptophan liable to be relatively deficient, but the associated pyridoxine deficiency[19] would prevent normal conversion of tryptophan to 5-hydroxytryptamine.[20] In African cardiomyopathy the male to female incidence is about 1:1.[21] Among women there is a definite tendency for the disease to occur not only in those who have babies but actually in association with pregnancy, especially multiple pregnancies, and more particularly post partum. It is interesting that pyridoxine deficiency is greater post partum than during pregnancy.[19] Thus, there is a parallel with the experimental situation, wherein the same severity of fibrosis as in the males was met only after three pregnancies in females, and further pregnancies were associated with still severer fibrosis.

Summary

The dietary production of a cardiomyopathy in rats is described. The tryptophan contents of the diet and plasma were low. Late supplementation with tryptophan, nicotinamide, or pyridoxine failed to prevent fibrosis, and possible reasons for the failure are discussed. Plasma levels of tryptophan correlated inversely with the severity of the cardiomyopathy. The severity of cardiac findings in females was associated with pregnancy rate. A possible relationship to African cardiomyopathy and a significance to cardiac disorders which are associated with disturbances of tryptophan metabolism is suggested.

Measurements of dietary tryptophan were performed by the National Nutrition Research Institute through the kind office of Dr. A. S. Wehmeyer.

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Case reports

Subacute bacterial endocarditis due to Hemophilus aphrophilus

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In 1940 Khairat[1] isolated a new species of Hemophilus in England from a patient with subacute bacterial endocarditis. He designated this *Hemophilus aphrophilus* Since then, 6 other cases of endocarditis due to this organism have been reported in the Western Hemisphere [2-4] In addition a case of brain abscess due to this organism was reported by Fager [6] This paper will present another case of subacute bacterial endocarditis due to *Hemophilus aphrophilus* According to King and Tatum [7] 41 strains of *Hemophilus aphrophilus* isolated from human infections had been received up to 1962, at the Communicable Disease Center United States Public Health Service, in Atlanta, Georgia

Case report

Mr R. C., a 47-year-old Chinese male, was admitted to Kaiser Foundation Hospital on Feb. 18 1964 with a 10-day history of fever malaise, headache and body ache. Four days before admission he had had occasional blood-streaked discharge from the left side of the nose and slight pain over the left side of the face. X-ray films of the sinuses revealed right maxillary sinusitis with mucosal thickening and polypoid changes which were slightly more prominent than those showing on films taken 1 year earlier The chest x-ray film was normal The first blood cultured at this time was negative. A complete blood count revealed the hemoglobin to be 12.3 Gm., hematocrit 35.5 per cent, white count 7,300 with 7 per cent bands, 61 per cent segments, 26 per cent lymphocytes and 6 per cent monocytes. The specific gravity of the urine was 1.020. Microscopic examination, sugar and protein were negative. The sinusitis was treated with erythromycin (Ilosone), 250 mg. every 4 hours for 3 days. However the temperature continued to spike to 103-104°F daily and the patient was hospitalized. There was no past history suggestive of rheumatic fever scarlet fever or diphtheria. He denied dental work or any trauma for the few months before his admission. In 1952, he was first told of a heart murmur during a physical examination elsewhere. In 1959 he had his initial visit to our clinic. At that time there was a suggestive systolic thrill at the aortic area on expiration. A Grade 3-4/6 rasping, harsh, diamond-shaped ejection systolic murmur was heard at the aortic area, with transmission to the neck. The second heart sound was single and was diminished at the aortic area. A Grade 2/6 apical systolic murmur of similar characteristics was also noted. The electrocardiogram revealed a normal sinus rhythm with the P R interval 0.16 second, QRS interval 0.08 second, slight elevated S-T segments in Leads II aV and V and small Q waves in Leads II III and aV An electrocardiogram taken on Jan. 19 1961 revealed deep S waves in Lead V and tall R waves in Lead V greater than 40 mm. There was a definite increase in cardiographic evidence of left ventricular hypertrophy when compared to the previous tracings. The patient had been given 1.2 million units of benzathine penicillin G (Bicillin) monthly from 1959 to 1963 In 1963 this was changed to oral penicillin, 250 mg twice day On admission the blood pressure was 130/86 mm. Hg pulse 86, and temperature 102°F H did not appear to be in acute distress. The only significant finding was the change in the heart murmur The aortic systolic murmur was Grade 1 2/6 and the apical pansystolic murmur was grade 3-4/6. Four more blood cultures were performed Studies included antistreptolysin O titer 50 units, fasting blood sugar 77 mg per cent, blood urea nitrogen 19 6 mg per

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cent, total serum bilirubin 0.85 mg. per cent, albumin 3.9 Gm. per cent, globulin 3.1 Gm. per cent, AG ratio 1.3/1, SGOT 18 units, SGPT 13 units, LDH 280 units, platelets 190,000, reticulocytes 1.7 per cent, and prothrombin time 70 per cent. Malarial smears were negative, and examination and culture of the urine were negative. Throat culture revealed many alpha hemolytic streptococci and Neisseria. There was an occasional colony of *Staphlococcus aureus* coagulase positive. The cardiac size and configuration was normal on the chest x-ray film.

On the seventh hospital day a petechia was noted on the left lower eyelid. Also a blood culture was first reported to be positive for a gram-negative coccobacillus, and four subsequent cultures were also positive for the same organism. This organism was later proved to be *Hemophilus aphrophilus*. The organism was sensitive to penicillin, terramycin, chloramphenicol, streptomycin, and polymyxin B sulfate. The patient became progressively anemic and the hemoglobin and hematocrit dropped from 12.3 Gm. and 35 per cent to 8.6 Gm. and 26 per cent, respectively. Two units of blood were given. The patient was given streptomycin 0.5 Gm. intramuscularly every 8 hours and 20,000,000 units of aqueous penicillin daily in a continuous intravenous drip. Probenecid (Benemid) 0.5 Gm. was also given four times a day. The temperature continued to spike to 101°F. daily in spite of therapy. On the fifth day of treatment, the penicillin was increased to 40,000,000 units daily. The organism growth was inhibited by 1:32 dilution of the patient's serum. On tube dilution, the organism was inhibited by penicillin, 0.38 units per milliliter, streptomycin 12.5 mcg. per milliliter, and oxytetracycline 6.5 mcg. per milliliter. The patient became afebrile 24 hours after the penicillin had been increased. Subsequent blood cultures were all negative. However, 21 days after initiation of the penicillin and streptomycin therapy, the temperature again spiked to 103 to 104°F. daily. Repeated blood cultures were negative. After 3 days of spiking temperature and chills, the penicillin and streptomycin were discontinued. The patient was then given methicillin (Staphcillin), 1 Gm. every 8 hours intravenously and tetracycline, 2 Gm. daily as a continuous intravenous drip. Twenty-four hours later the temperature became normal and remained so until discharge on the forty-seventh hospital day. Methicillin was discontinued after 10 days, and after 13 days the intravenous tetracycline was discontinued. He was then given tetracycline 2 Gm. per day orally and received this for another 30 days without side effects. He has remained afebrile and asymptomatic. During his last visit here on June 24, 1964, a Grade I apical lift was noted. No systolic thrill was felt. A Grade 2-3/6 diamond-shaped ejection systolic murmur was present at the aortic area and was transmitted to the neck. A Grade 2-3/6 systolic murmur of similar characteristics was noted at the apex. There was also a decrescendo diastolic blowing Grade 1/6 murmur along the left sternal border. On cardiac fluoroscopy the cardiac transverse diameter, main pulmonary artery segment, and right ventricle were normal. The left ventricle clearance angle was 75 degrees. The barium swallow was negative for left atrial enlargement and the right pulmonary artery was of normal size and pulsation. The electrocardiogram at this time showed no essential changes from that taken on Jan. 19, 1961, and on admission on Feb. 18, 1964. The patient was returned to his previous sedentary occupation as an engineer on June 29, 1964.

Bacteriology

Hemophilus aphrophilus is a gram-negative, nonmotile, nonsporing, nonacid-fast, coccobacilli 0.5 to 1.0 micron in length when freshly isolated. After repeated subculture it becomes more rod shaped. It is dependent on X factor (hemin) when grown in air. V factor (diphosphopyridine nucleotide) is not needed for growth. The characteristics of this organism are described by different authors.[1,2,7] King and Tatum[7] show the very close relationship of *Hemophilus aphrophilus* to *Actinobacillus actinomycetemcomitans* and state that the present classification of these two species in two different genera was most unsatisfactory.

Discussion

Streptococci of the viridans type are by far the most common cause of bacterial endocarditis. The hemophilus species causes only a small percentage of infection. Between 1936 and 1963, only 36 cases of Hemophilus endocarditis were reported.[4,9] The 8 cases of subacute bacterial endocarditis caused by *Hemophilus aphrophilus* are summarized briefly in Table I. The ages of the patients ranged from 9 to 66 years. Only one out of the 8 was reported in the preantibiotic era, and this patient did not survive. Of the other 7, there were 6 survivors. All but one had a pre-existing cardiac lesion, which was probably rheumatic in origin. There are certain similarities between our patient, that of Keith and Lyon, and that of Witorsch and Gorden. These patients were treated initially with penicillin and streptomycin and responded well. However, the fever returned on the seventeenth day in Keith and Lyon's patient, on the nineteenth day in Witorsch and Gorden's Case No. 3, and on the twenty-first day in our patient. Repeat blood cultures were negative. The return to the spiking temperatures was attributed by Keith and Lyon to a genitourinary infection by *Pseudomonas aeruginosa*. Streptomycin was then discontinued and tetracycline and colistin were added to the regimen. Witorsch and Gorden did not speculate as to the possible cause of

Table I Reported cases of Hemophilus aphrophilus endocarditis

Case	*Age (yr.), Sex*	*Cardiac lesion*	*Precipitating factor*	*Treatment*	*Survival*
Khairat[1] (1940)	28, F	Undetermined	Undetermined	Sulphanilamide followed by 2 sulphanilyl-aminopyridine	No
Tosbach and Bain (1958)	47 M	RHD AS	Undetermined	Terramycin aureomycin, chloramphenicol followed by penicillin	No
Vargas, Gilabert, Kohan[3] (1962)	9 F	RHD MR or VSD	Undetermined	Penicillin and streptomycin	Yes
Keith and Lyons[4] (1963)	66 M	RHD MR and MS	Dental extraction	Penicillin and streptomycin followed by penicillin, tetracycline, and colistin	Yes
Witorsch and Gorden[5] (1964)	28, F	RHD MR and MS	URI	Penicillin and streptomycin	Yes
Witorsch and Gorden[5] (1964)	35 M	RHD MR, MS AR	Dental cleaning	Penicillin and streptomycin	Yes
Witorsch and Gorden[5] (1964)	25 M	RHD? MR	Sore throat cortisone treatment for dermatitis	Penicillin and streptomycin with chloramphenicol added later	Yes
Dung and Lin (1964)	47 M	RHD AS	URI and sinusitis(?)	Penicillin and streptomycin followed by tetracycline and methicillin	Yes

AS: Aortic stenosis. *MR:* Mitral regurgitation *MS* Mitral stenosis. *RHD:* Rheumatic heart disease *VSD* Ventricular septal defect. *URI* Upper respiratory infection

the return of the fever and chloramphenicol was added. In our case no cause could be proved but drug reaction or the development of resistance of the organisms to penicillin was considered The penicillin and streptomycin were then discontinued and treatment with tetracycline and methicillin was initiated The three patients responded favorably

Summary

A case of subacute bacterial endocarditis due to *Hemophilus aphrophilus* is described Seven other cases reported from 1940 to 1964 are summarized briefly The cases have come from different parts of the world including Canada, Chile, England Hawaii and the continental United States. A pre-existing cardiac lesion is a probable prerequisite for this infection Penicillin and streptomycin seem to be the treatment of choice. The case presented was treated successfully with penicillin and streptomycin followed by tetracycline and methicillin

We gratefully acknowledge the help of Dr John Kim in the management of the patient, and the Communicable Disease Center United States Public Health Service, Atlanta, Georgia for their identification of the organism.

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Transient abnormal Q waves during coronary insufficiency

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The abnormal Q wave is usually accepted evidence of myocardial infarction. Occasionally abnormal Q waves are present in the absence of myocardial infarction, as in muscular dystrophy, amyloid replacement of the myocardium, or metastasis to the heart. Isolated reports have shown Q waves appearing during a bout of angina or coronary insufficiency and disappearing after cessation of the attack. The following is a report of the occurrence of transitory abnormal Q waves during a bout of angina or coronary insufficiency.

Case history

A 72-year-old white man was admitted to the Morrisania City Hospital for the seventh time on Dec. 9, 1963, because of recurrent chest pain. His first admission had been in 1948, when, while at work, he had suffered tearing substernal chest pain that radiated through to the back. The diagnosis was acute myocardial infarction. Since then he has had recurrent bouts of chest pain brought on by exertion or emotional stress; the pain was usually relieved promptly by nitroglycerin. Several episodes persisted and were not relieved by nitroglycerin. He was hospitalized nine times for these episodes, which were diagnosed as acute coronary insufficiency. For 2 years prior to the last admission he had had frequent chest pain when walking one and one-half blocks on an incline; the pain was quickly relieved by nitroglycerin.

Six days prior to the present admission he had had a severe attack of substernal pain and dizziness on exertion which was relieved by nitroglycerin in several minutes. For the next 5 days, angina recurred whenever he walked one or two blocks and was relieved by nitroglycerin. For 24 hours prior to admission angina occurred every few hours at rest.

He had had typhus fever at age 27. During the winters for the preceding 40 years he had had bronchitis, and for the last 15 years his sputum had occasionally been streaked with blood.

Examination on admission showed an alert man in no acute distress. The temperature was 98°F. The pertinent physical findings included mild A-V nicking in the fundi, flat neck veins, point of maximum impulse of the heart in the fifth intercostal space in the mid-clavicular line, the pulmonic component of the second sound greater than the aortic component, rhythm regular, no murmurs or gallop, no hepatic or splenic enlargement, and no edema; blood pressure 150/100 mm. Hg.

Laboratory findings included: hematocrit of 43 per cent, white cell count of 8,800 per cubic millimeter, normal differential, blood urea nitrogen 18 mg. per cent, fasting blood sugar 92 mg. per cent, VDRL nonreactive. X-ray examination of the chest was negative except for calcified right hilar nodes. The serum glutamic oxalacetic acid transaminase was 18 units on the day after admission, 36 units 2 days later, and 52 units 6 days after admission; it then declined to 10 units. An electrocardiogram (Fig. 1) showed regular sinus rhythm, a diphasic T wave in Lead II, inverted T waves in Leads III

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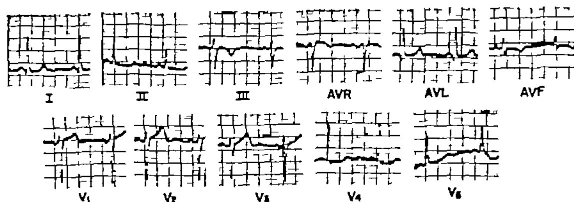


Fig. 1. Electrocardiogram on admission. Regular sinus rhythm, diphasic T waves in Lead II, inverted T waves in Leads III and AVF, slight depression of the R-T segments in lead V_6.

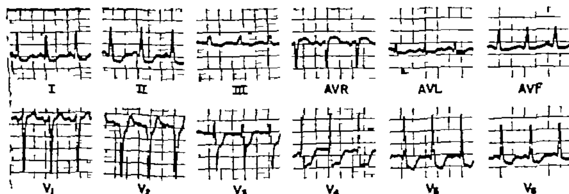


Fig. 2. Electrocardiogram recorded 5 minutes after onset of pain. Sinus tachycardia, depression of the R-T segments in Leads I, II, and AVL, marked in Leads V_3-V_6, with inverted T waves in Leads V_4, V_5, and V_6. Lead V_1 has a small initial r wave, there is no r wave in Lead V_2 with a notch on the initial downstroke of the S wave, a prominent Q wave, 1 mm. in depth, followed by an r wave measuring 3.5 mm. appear in Lead V_3.

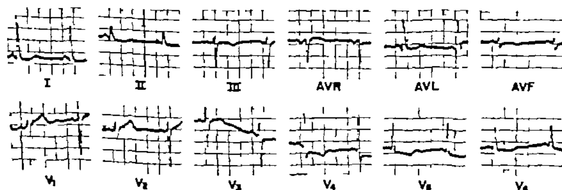


Fig. 3. Electrocardiogram recorded 12 hours after that shown in Fig. 2. Regular sinus rhythm. T is diphasic in Leads II, V_4, V_5, and V_6. T wave is inverted in Leads III and AVF. Note disappearance of Q waves previously present in Leads V_2 and V_3 and normal progression of the R waves in these leads.

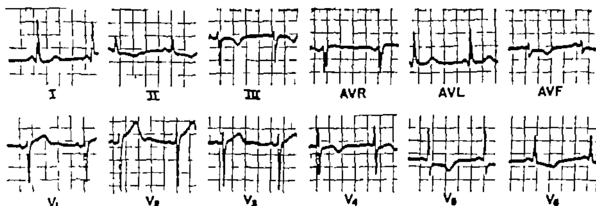


Fig. 4. Electrocardiogram recorded 5 days after that shown in Fig. 3. Regular sinus rhythm, further inversion of the T waves in Leads II, III, AVF, V_4, V_5, and V_6.

and AVF and slight R-T depression in Lead V_6.

Clinical course. Approximately 12 hours after admission an episode of typical chest pain occurred. The blood pressure was 180/100 mm. Hg. An electrocardiogram 5 minutes after the onset of pain (Fig. 2) showed sinus tachycardia, depression of the R-T segments in Leads I, II, and AVL, marked in Leads V_1-V_4, and Q waves in Leads V_1 and V_2. Nitroglycerin relieved the pain in a few minutes. An electrocardiogram taken 12 hours later (Fig. 3) showed disappearance of the Q waves in Leads V_1 and V_2, the marked R-T depression had largely disappeared, and the T waves were now diphasic in Leads V_1-V_6. The electrocardiogram recorded on the following day (Fig. 4) showed further inversion of the T waves in Lead II, III, AVF, and V_4-V_6, but no Q waves. Subsequent electrocardiograms showed little additional change.

The highest temperature was 100.8°F. on the third day of hospitalization. Anticoagulation had been started on admission with 75 mg. of heparin subcutaneously every 6 hours and was maintained with Coumadin. Mild, brief attacks of chest pain recurred during the first week. Anginal attacks recurred during the next 2 weeks, often at stool, and were relieved by nitroglycerin. After 3 weeks the patient was ambulated; subsequently episodes of angina occurred almost daily and were relieved by nitroglycerin.

Discussion

There have been several reports in the literature of transient, abnormal Q waves in the absence of myocardial infarction. This subject was recently reviewed by DePasquale, Burch and Phillips.[1] Roessler and Dressler[2] also observed transient Q waves during anginal attacks similar to those of myocardial infarction. Segers, Regnier and Delatte[3] observed a deep Q wave in Lead V_4 during exercise in a patient with angina. Neither the control nor the postexercise tracing taken 4 minutes later showed a Q wave. They also observed chest pain and fluctuating T wave changes in a 40-year-old person who developed anaphylactic shock after the ingestion of eggs. Two weeks later the patient developed a transitory Q wave in Lead V_2. Rosenfeld, Silverblatt and Grishman[4] reported transitory QS waves in Lead V_1 during an asthmatic attack. They believed that the Q wave was due to a change in the electrical position of the heart and coronary insufficiency.

Rubin, Gross and Arbeit[5] observed a patient with healed myocardial infarction with a residual abnormal Q wave limited to one precordial lead. On four separate occasions during bouts of tachycardia there were widespread abnormal Q waves in both the frontal and horizontal plane leads, which promptly disappeared with cessation of the tachycardia. They ascribed these transient Q-wave changes to either reversible ischemia of the myocardium or to aberrant conduction during tachycardia.

Transitory abnormal Q waves in the absence of evidence of myocardial infarction at necropsy have been reported. In the two cases reported, Goldman, Gross and Rubin[6] attributed these Q waves to a severe metabolic stress due to hypoglycemia, anemia, and ischemia in one and to shock and possible adrenal insufficiency in the other. Fulton and Marriott[7] reported an instance of acute pancreatitis in which a QS pattern developed in Leads

V_1 and V_2, along with S-T segment elevation in Leads I, AVL, and V_1-V_4. Two days later the R waves reappeared in Leads V_1 and V_2. At autopsy no evidence of myocardial infarction was found.

Transitory Q waves have also been produced experimentally. Bayley and La Due[9] occluded the coronary artery of a dog for 50 minutes and noted the development of a progressively deepening Q wave after 35 minutes of occlusion which disappeared within 15 minutes after release of the occlusion. Zuckerman and co-workers[4] demonstrated the disappearance of abnormal Q waves after blood transfusion and restoration of blood pressure in dogs with experimental myocardial infarction. Gross and associates[10] produced transitory abnormal Q waves after coronary artery ligation in 7 of 19 dogs. When the ligature was released the Q waves promptly disappeared. No evidence of gross muscle necrosis

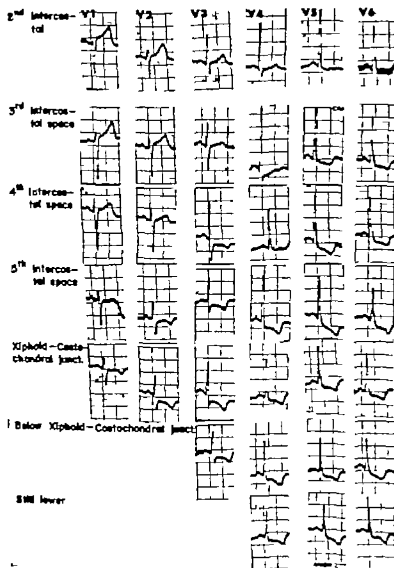


Fig. 5. Electrocardiogram recorded 4 days after that shown in Fig. 3. Leads V_1-V_6. *Upper four rows of tracings, from top downward:* Second, third, fourth and fifth intercostal spaces, respectively. *Fifth row:* Junction of xiphoid sternum and costochondral junction. *Sixth row:* Below the level of the xiphoid sternum and costochondral junction. *Seventh row:* Lowest tracing, lower than the level of the xiphoid sternum and costochondral junction.

was present on macroscopic and microscopic examination of these hearts.

In the presently reported case several questions arise. The first is whether the changes could have resulted from a shift in the electrical position of the heart. Exploration of the entire chest wall 6 days after the onset of pain showed no abnormal Q waves (Fig 5) The deep Q waves were present in contiguous horizontal leads. Rotation does not produce such abnormal Q waves in V leads. Fig 2 shows an R wave of good size in Lead V_1 a notched QS wave in Lead V_2 and an abnormal Q wave in Lead V_3.

The second question is whether the patient had acute myocardial infarction In favor of such a diagnosis is the development of an abnormal Q wave, the rise in temperature to 100 8°F 24 hours after the appearance of the Q wave and the elevated serum glutamic oxalacetic acid transaminase level to 52 units 5 days after the appearance of the Q wave The subsequent inversion of the T waves in Leads V_4 to V_6 supports this view Against the diagnosis of acute myocardial infarction is the transitory nature of the Q wave. The pain associated with the Q wave was typical of that of his previous anginal attacks, in character severity and distribution and was promptly relieved by nitroglycerin as were his other attacks. The S-T segment depressions were characteristic of angina or coronary insufficiency These were also gone within 12 hours. The rise in the serum glutamic oxalacetic acid transaminase level was minor but may have been due to miliary myocardial necrosis. We can neither rule out nor rule in the presence of myocardial infarction in this patient although the clinical course favored a diagnosis of angina or coronary insufficiency

The transitory Q waves in the mid precordial leads during chest pain suggest electrophysiologic inertness of the myocardium similar to that occurring in myocardial infarction The subsequent disappearance of the abnormal Q waves suggests that this area of myocardium was temporarily inert (electrically silent) [1] The appearance and disappearance of the S-T segment depression shows that other parts of the myocardium were also ischemic at the time. The area of myocardium that led to the development of the Q waves was probably more severely ischemic, resulting in a loss of electrical activity of this area This change was also reversible, as indicated by the return of normal electrical activity in this area evidenced by a return of the R wave in Leads V_2 and V_3.

This report substantiates the clinical and experimental observations made by us and others[1-4,6-10] of the appearance of abnormal Q waves in cases of transitory myocardial ischemia without myocardial infarction.

Summary

A 72 year-old man with arteriosclerotic heart disease and chronic coronary insufficiency of many years duration developed severe recurrent anginal attacks. During an attack of chest pain abnormal Q waves developed in Leads V_2 and V_3, but promptly disappeared with relief of the pain The serial electrocardiographic changes and the clinical course were those of angina or coronary insufficiency but myocardial infarction could not be ruled out. We believe that these Q waves were due to transitory ischemia of the myocardium

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Thromboangiitis obliterans

Simultaneous quadrilateral acute ulcerations in thromboangiitis obliterans. Follow-up studies of a case after 27 years

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In 1937 Lattauer and Wright[1] published a study of an unusual example of thromboangiitis obliterans in a 39-year-old man who had developed simultaneous gangrenous lesions of all four extremities. No previous reports of quadrilateral acute lesions involving all extremities at the same time could be found. Characteristically, the acute lesions of this disease develop serially, and some may heal while others develop. During subsequent experience of 27 years, involving several thousand cases of peripheral vascular disease, we have not seen a similar case of thromboangiitis obliterans, although simultaneous quadrilateral gangrene has been encountered in several other conditions including frostbite and acute ergotism. This report was presented in detail in the AMERICAN HEART JOURNAL of October 1937, and will be reviewed briefly here.

Case report

The patient's complaint of a series of ulcerations involving the fingers and toes had begun 2½ years prior to the time when we first saw him on Feb. 23, 1937. A few of these ulcerations had healed, but, generally, they had become increasingly painful and numerous. A photograph of these is shown in the original report. There was no suggestive etiology except the fact that he has smoked approximately 20 cigarettes a day for many years. The acute ulcers were characteristic of thromboangiitis obliterans with a zone of redness surrounding a necrotic, often black, crusted, purulent area from which pus could frequently be expressed. The left foot was swollen; dependency of the extremities produced marked rubor; elevation produced blanching to a "dead white." Tests showed that the left ulnar and both dorsalis pedis arteries had markedly reduced functional capacity, and that the damage was confined mostly to the more peripheral vessels, especially the digital branches. Arteriographic studies were performed using thorium dioxide sol, which was then in common use. The x-ray films as shown in the original report clearly demonstrated that in the upper extremities the arteries were normal to the wrists, but that distally the smaller branches were diffusely and severely damaged, with multiple occlusions scattered irregularly throughout the vascular tree. Attempts to carry out such studies in the lower extremities were not successful, but the clinical picture was so similar that it appeared that the same type of process was taking place.

The therapeutic regimen consisted of total abstinence from tobacco, and fever therapy with the fever being induced by small, carefully controlled doses of typhoid vaccine intravenously (In our experience still the most effective treatment for the acute gangrenous ulcers of thromboangiitis obliterans). The first dose was five million organisms, and this was increased slowly to induce an increase in temperature of 2 to 3 degrees centigrade at intervals of 48 to 72 hours. Healing began within a week, and the patient was discharged at the end of 7 weeks, with all ulcers painless and healed. Five weeks later he was back at work, free from symp-

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toms. The results were not exceptional and have been duplicated many hundreds of times with this therapy which is in constant use on our service today. At the same time, the risk of recurrence with the resumption of smoking is well established, and this was emphasized to this patient. He was followed for a few months and had no further trouble.

In September 1964, 27 years later at the age of 66, the patient was seen by one of us (G. B.) in Boca Raton, Florida, complaining of a sudden onset of circumoral numbness and weakness, and numbness of the base of the left thumb. There were no other complaints. He denied weakness, confusion, ataxia, dizziness, visual disturbances or headache, diabetes mellitus, and the use of alcohol or tobacco. During the previous 4 months he had lost 15 pounds of weight, despite a good appetite. He had experienced no nausea, vomiting, change in bowel habits (1-2 stools daily), melena, jaundice, fever or malaise. He had not used antacids. There were no symptoms of hyperthyroidism.

Physical examination. The blood pressure was 150/82 mm. Hg. Pulse was 72 and regular. There was no local or regional enlargement of the nodes. Examination of the ears, nose, mouth, and throat showed these to be within normal limits. Eyes: Muscular action—N. Sclerae and conjunctivae clear. Pupils reacted to light and accommodation. fundi Grade II arteriosclerotic changes. There were no plaques of Hollenhorst. Pulsations were strong and equal in the carotid arteries no thrills or bruits were present. Thyroid was normal. The lungs were clear to percussion and auscultation movement was normal. The heart showed regular sinus rhythm, rate 74 there was no enlargement and there were no murmurs. The abdomen was normal to palpation abdominal x-rays films revealed a small densely radiopaque liver and spleen. A thorough neurological examination revealed no objective abnormality. Examination of the extremities revealed no abnormalities, except for healed old scars of the fingers and toes (Fig. 1). The pulses were studied in detail, with plethysmography where feasible, by Dr. Hugh Gilmore III of Jackson Memorial Hospital, University of Miami Medical School. The findings are given in Table I. Oscillometric readings were normal, except that each foot was less than one unit (Collens). There was no pallor on elevation or rubor on dependency. The time for color return and venous refill in the feet was less than 10 seconds, a normal value. Capillary refilling after finger blanching (Lewis) was less than 3 seconds, also a normal value. Digital plethysmograms are shown in Fig. 2. Values for the digits on the right were slightly less than the values for the digits on the left, but were still considered to be within normal limits.

Laboratory studies. Laboratory studies in October 1964 included the following, which were within normal limits except where noted. ECG. Hemoglobin 13.9 Gm. hematocrit 35. WBC. Differential. Urinalysis. Determination of blood urea nitrogen and

Table I

Pulses	*Right*	*Left*	
Carotid	N	N	(palpation)
Brachial	N	N	
Radial	N	N	
Ulnar	N	A	
Femoral	N	N	
Popliteal	N	N	
Posterior tibial	N	N*	(palpation)
Dorsal pedis	D	F	(palpation)

*Confirmed by Allen test.
N Normal D Diminished. F Faint. A Absent.

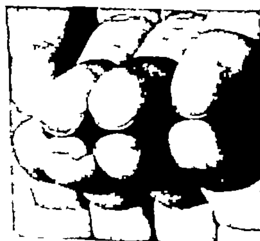


Fig. 1. Completely healed fingers. Both the fingers and the toes have remained healed for the past 27 years.

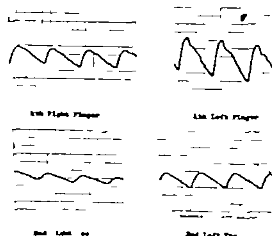


Fig. 2. Digital plethysmograms. See text.

fasting blood sugar. Calcium. PO. BSP. Alkaline phosphatase. Bilirubin. Prothrombin time. Cephalin flocculation. Protein electrophoresis: total protein albumin 2.8Gm. (normal, 3.12-5.2 Gm.) globulins Alpha I .59 Gm. (normal, .12-0.40 Gm.) alpha II beta gamma. Stool for occult blood. VDRL.

Progress note. The local numbness and weakness disappeared within 2 weeks and has not recurred. The patient is asymptomatic and his weight has stabilized at 185 pounds. No satisfactory explanation for this apparently transient syndrome was found.

Discussion

This patient is of particular interest for several reasons. He developed his symptoms at the age of 36, relatively late in life for thromboangiitis obliterans, but not beyond the extreme limits. This may have been due in part to the fact that although he smoked for many years he was never an extremely heavy smoker. His original skin ulcerations were characteristic of thromboangiitis obliterans, showing much more of an inflammatory response than those usually seen in nondiabetic atherosclerosis. The arteriograms showed the classic segmental involvement of major vessels. This has been called the "moth-eaten" pattern of the medium-sized and small arteries, and illustrates the centripetal involvement typical of this disease. The response to treatment, comprising abstinence from tobacco and controlled intravenous typhoid vaccine, was prompt, with complete healing in a few weeks. He did not resume smoking and there has been no relapse in 27 years. Clinically there has been a regression of the previous state of his vascular disease during this long period. This is to be expected with properly treated thromboangiitis obliterans, but not with atherosclerosis obliterans.

All of this is of interest in the light of the recent reactivation of the question of whether thromboangiitis obliterans is a distinct clinical entity or whether it is a manifestation of atherosclerosis. As this discussion has progressed it is clear that the majority of those who have had wide experience with the clinical manifestations of vascular disease believe that this entity is distinct from atherosclerosis obliterans, whereas a few whose experience has been largely in the field of pathology reserve doubts as to this position.[1,2] After 35 years of experience as head of a large vascular service (I.S.W.), we believe that there is no doubt that thromboangiitis obliterans is a specific disease depending on at least dual etiological factors for its development and progression. One may be hereditary but does not appear to be so and is not well understood. It is not a sensitivity in the usual allergic sense and much further work needs to be carried out to clarify this mechanism. It is essential that such a factor be present in order to explain the fact that tobacco is a highly toxic agent for a selective few persons, whereas millions of others use it heavily without developing this disease.

The second factor is tobacco. Without this the disease probably would never occur, although there have been a few cases reported in nonusers, mostly many years ago, which made the older literature confusing in this regard. A review of many of these cases indicates that they were wrongly diagnosed and in our personal experience they have been commonly confused with cases of diabetic gangrene. When tobacco is no longer used, the disease characteristically becomes quiescent, without further progress, and the lesions heal. In these patients, the resumption of smoking, even years later, results in reactivation. Within 1 to 4 months, a new lesion can be expected to occur. This has been seen to happen whether the patient began to chew tobacco or to smoke, however mildly, and with a variety of filter as well as regular cigarettes. As added evidence of this relationship, one of us (I.S.W.) has seen two typical cases of thromboangiitis obliterans with open necrotic ulcers in young boys, one 11 years old and the other 13 years old. One of these was seen in Cuba and one in Puerto Rico. They were both street urchins who, at the age of 4 or 5 years, had acquired the habit of smoking by picking up discarded cigarette butts in the streets.

It appears that confusion responsible for the recent questioning of this clinical entity may have arisen because characteristically most of these patients live to their middle or later years before either undergoing major amputations or dying, so that by the time their vessels reach the pathologist, a recognizable degree of atherosclerosis has developed. It may be

that this occurs somewhat earlier because of the previous vascular damage. It has also been demonstrated that if one searches assiduously, one can find evidence of atherosclerosis or something resembling it in the arteries of a large percentage (70 per cent plus) of young men (20 to 30 years of age). Therefore, it is not surprising that such changes have been found by careful pathologic examination in a large percentage of patients with thromboangiitis obliterans. This does not necessarily justify the conclusion that the inflammatory lesions characteristic of this disease are a manifestation of atherosclerosis. The explanation for the seeming rarity of this condition in recent years, especially in the findings of laboratories of pathology, is probably the increased recognition of the role of tobacco in affecting the circulation, and the insistence by physicians that patients who show early signs of any vascular disease stop smoking permanently. The disease then ceases to progress, and the patients do not require subsequent hospitalization and amputation. This is a sharp reversal from the situation we encountered 35 years ago when in many hospitals these patients were given the special privilege of smoking because of the agonizing pain they suffered. It is now the exceptional patient who because of inability to stop smoking progresses to amputation regardless of sympathectomy or any other form of surgical or medical treatment. Since women have smoked more excessively in recent years, the proportionate incidence of fresh cases in women has increased markedly. Formerly the proportion of males to females was 30 to 1. In the past 5 years, we have seen this change to approximately 6 to 4.

Another aspect of interest in this case is the fact that the patient received at least four injections of thorium dioxide intra-arterially and that this is still deposited in his liver and spleen after 27 years. Thorium dioxide was one of the very best radiopaque substances ever to be developed and the incidence of immediate reactions was practically nil. However, it is radioactive and after it had been in use for some years, cases were reported in which malignancy developed in either the liver or the spleen, or at the site of injection if there was leakage of the material into the surrounding tissues. We do not know of any cases of malignancy arising from studies in cases of thromboangiitis obliterans. The material, however, fell into disuse and other substances were used which were believed to be less dangerous. Many patients who received thorium dioxide have lived for years without any difficulty attributed to it, and have died of other causes. This patient is still living and healthy after 27 years. Numerous liver function tests have failed to show significant evidence of damage.

Summary

The case of a patient with thromboangiitis obliterans who had quadrilateral gangrene of the digits was reported in 1937. His disease became quiescent after cessation of smoking and intravenous typhoid vaccine. During the interim of 27 years, he has abstained from smoking and there has been no reactivation of his disease. Clinically there has been a regression of his vascular lesions during this time. He represents the ideal in terms of treatment and response. In 1937, as part of the preliminary examination, he received at least four intra-arterial injections of thorium dioxide sol for visualization studies, and in 1964 this material was visualized as deposited in the liver and spleen. There was, however, no evidence of liver or spleen dysfunction or disease. Our experience with this patient and many others leads us to the conclusion that thromboangiitis obliterans is a distinct disease, although it is sometimes wrongly diagnosed. The reasons for this conclusion and for the confusion of this disease with atherosclerosis obliterans have been discussed.

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Clinical pathologic conference

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Clinical history

The patient, a 51-year-old Negro woman, was hospitalized on May 24, 1964, with a chief complaint of "heart trouble." Four days prior to admission she had noted irregular palpitation and increasing shortness of breath, with orthopnea and cough productive of yellow sputum. She had noted dependent edema for about a month. Along with the above-mentioned symptoms she had also developed nausea, vomiting, and diarrhea. Because of this she stopped digitalis and on the day of admission her diarrhea had ceased.

Past medical history was complex in that she had had a history of bronchial asthma dating to 1945 which had been seasonal at first, but had not been in recent years. In 1945 she had had thyrotoxicosis and had undergone a subtotal thyroidectomy.

In 1956, while being evaluated for her asthma, she was noted to have an enlarged heart and, on chest film, "prominent vascular markings and prominent left heart border including PA segment." The hilar markings were thought to be suggestive of Boeck's sarcoid. Films of the hands and feet were negative. An OT 1:10,000 was negative, but 1:1,000 was positive. An electrocardiogram was interpreted as showing left ventricular strain (May 31, 1956). Digitalization produced marked improvement in the dyspnea and wheezing.

In 1959 she was admitted to the hospital for evaluation of cardiomegaly, hepatosplenomegaly, edema, and asthma. Biopsy of a right scalene fat pad showed a normal node with no evidence of sarcoid. Skin tests for tuberculosis and fungi were negative. A chest film and cardiac fluoroscopy showed primarily left ventricular enlargement, with some slight enlargement of the left atrium. An electrocardiogram (April 29, 1959) showed occasional ventricular premature contractions, left ventricular strain, and abnormal P waves in the right precordial leads suggestive of right atrial hypertrophy. She was discharged without a diagnosis being made of the type of heart disease present. She had had three episodes of bronchopneumonia since 1959. Pneumococci were cultured on all admissions and she responded to penicillin each time.

In November, 1962, a fourth-year student heard a Grade 2 apical presystolic murmur with the patient in the left lateral recumbent position, and an accentuated pulmonary second sound. A cardiac series showed generalized cardiac enlargement, chiefly of the left atrium. An electrocardiogram (Nov. 15, 1962) was suggestive of pulmonary disease, and the S-T and T changes were thought to be consistent with digitalis effect or coronary insufficiency or both. In October, 1963, she became more dyspneic and pulmonary function studies revealed a marked reduction in the vital capacity without spirographic evidence of airway obstructive disease. At rest, arterial O_2 and CO_2 tensions were 60 and 39 mm. Hg. After standard exercise, PO_2 was 70 and PCO_2 was 34.

She was started on prednisone which gave some improvement in her situation, and this was continued until April, 1964. Her digitalis was continued until she stopped it in May, 1964.

Family history. One sister had "asthma and heart trouble."

Physical examination. The blood pressure was 120/80 mm. Hg, pulse was 120 (irregular), respirations were 32, and temperature was 97°F. The patient, a middle-aged Negro woman, was sitting upright in bed in moderate respiratory distress. The neck veins were distended with the patient at a 40-degree angle. There were well-healed thyroidectomy and right-scalene-node-biopsy scars. The chest was symmetrical. The lungs were clear to percussion but there were bilateral basilar râles and inspiratory and prolonged expiratory wheezes. There was a left parasternal heave during cardiac systole. There was a grossly irregular rhythm, with a loud M_1 and

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P₂. No murmurs were noted The edge of the liver was palpable 4 cm below the right costal margin There was 4+ pitting edema of the ankles

Laboratory data included a cloudy acid urine with a 1+ albuminuria and a specific gravity of 1.004 Microscopic examination showed 10 to 15 WBC and 1 to 3 RBC per high-power field Hemoglobin was 13.2 Gm. per cent WBC 6,050 with 63 per cent neutrophils, 35 per cent lymphocytes 1 per cent eosinophils and 1 per cent monocytes Blood urea nitrogen was 7 mg per 100 ml and blood glucose was 70 mg per 100 ml. serum sodium was 135 serum potassium 3 4 serum chlorides 89 and bicarbonate content 26 mEq per liter Total bilirubin was 1.8 mg per 100 ml with a direct fraction of 0 5 mg Serum albumin was 3.3 Gm and globulin was 3 2 Gm Serum calcium was 8 5 and phosphorus was 3 1 mg per 100 ml Serologic test for syphilis was nonreactive. Other values included SGOT 40 protein-bound iodine 6 μg total cholesterol 142.

Cardiac fluoroscopy showed left atrial and right ventricular enlargement. Several electrocardiograms showed atrial fibrillation with occasional ventricular ectopic beats and digitalis effect and/or coronary insufficiency

A right heart catheterization was performed on June 5 1964 The values obtained are shown in Table I

With the patient on bed rest salt restriction, and diuretics, the peripheral edema gradually improved however she continued to show considerable pulmonary congestion She continued to complain of nausea, but her digitalis was reinstated on May 26 without exacerbation of her symptoms

On June 17 1964 the serum electrolytes showed sodium 126 mEq per liter potassium 3 0 chlorides 84 and bicarbonate content 22

On June 20 after an uneventful morning the patient got up to use the bedpan collapsed at the bedside, and was pronounced dead at 4 15 P.M.

Clinical discussion

DR. MAUCK This case is unusually interesting in three respects. The present illness and physical examination are straightforward and suggest a diagnosis on first reading By contrast, the past medical history is confusing with several apparent contradictions Finally the catastrophic event leading to the patient's death warrants further exploration

This patient was hospitalized with a chief complaint of heart trouble Four days prior to admission she had noted irregular palpitations increasing shortness of breath orthopnea and cough These symptoms suggest congestive heart failure as do the nausea and vomiting The yellow sputum raises the possibility of a pulmonary infection The diarrhea which was present a few days prior to admission soon ceased on admission possibly because of the discontinuation of digitalis. Physical examination confirmed the diagnosis of congestive heart failure The patient was sitting upright in bed in respiratory distress her neck veins were distended even in this position Examination of the lungs revealed bilateral basilar râles and prolonged inspiratory wheezes. Examination of the heart showed a right ventricular heave a grossly irregular rhythm loud first heart sound and an accentuated pulmonic second sound Interestingly no heart murmurs were heard The liver was palpable and edema was marked The physical findings, the low serum sodium and chloride and the slight elevation of the total bilirubin to 1 8 all suggest congestive heart failure The loud first heart sound accentuated pulmonic second sound and the absence of any left ventricular enlargement by physical examination are particularly notable This patient was in congestive heart failure, with involvement predominantly of the right side of the heart

There is a history of bronchial asthma, beginning in 1945 All wheezing is not bronchial asthma and considering the enlarged heart and the congestive heart failure now present one might think this symptom even in 1945 was a manifestation of cardiac disease She also had thyrotoxicosis in 1945 and underwent subtotal thyroidectomy Recently however her protein-bound iodine was 6 micrograms per 100 milliliters. She was brought into the hospital and evaluated for asthma in 1956 and there are several points of interest connected with this hospitalization

Table I Catheterization findings

	Pressure (mm Hg) S/D	Pressure (mm Hg) Mean	Volumes per cent oxygen	Sat ration ( )
RA	16/9 17/9	11 13	7 3	40
RV	89/17			
PA	112/34	70		
Wedge	—	27		
BA	135/90	104		91

Cardiac output 2 L. per minute



Fig. 1. Chest film taken in 1956 indicates cardiomegaly principally of the right side. The fullness in the right hilum was variously interpreted as sarcoid and increased vascular markings.

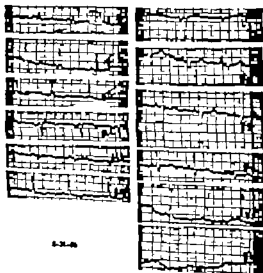


Fig. 2. ECG taken in 1956 was originally interpreted as indicating left ventricular strain but Dr. Mauck has interpreted it as showing left atrial enlargement and nonspecific S-T T changes.

The posteroanterior film of the chest was said to suggest Boeck's sarcoid. On reviewing the films, I do not see sarcoid. The bilateral mediastinal adenopathy frequently present in sarcoid is absent. There is no infiltration of the lung parenchyma. The heart is enlarged, the apex has the configuration of a sheep's nose and suggests the presence of right ventricular enlargement. Dr. Neal, would you comment on this.

DR. NEAL. Comparison of this film (Fig. 1) with one from 1952 shows a minimal increase in cardiac size. The findings are those of a right-sided change and the cardiomegaly does not suggest isolated left ventricular preponderance. The question of sarcoid was probably raised because of fullness of the right hilum. I think that this represents vascular markings and a prominent right hilum.

DR. MAUCK. An electrocardiogram was taken at this time (Fig. 2). This ECG was interpreted as showing left ventricular strain but I disagree with the interpretation. Even by the most lax criteria of left ventricular hypertrophy, for example, an R_5 and an S_1 of 35 mm. or more, we do not have evidence for such a diagnosis. The mean QRS vector in the frontal plane is +80 degrees. I think that the most important finding in this electrocardiogram was not commented upon in the protocol and that is the broad based P wave in Lead I. When we measure its amplitude we see that it is approximately 0.12 or 0.13 second. Definite notching is present and the P-R segment is within normal limits. We also notice in Lead V₁ a sharp late negative deflection of the P wave which strongly suggests left atrial enlargement.

The patient had had three episodes of bronchopneumonia since 1956. Pneumococcus was cultured on all admissions. In 1959 she was readmitted because of cardiomegaly, hepatomegaly, edema, and asthma, and I assume that there was still strong suspicion of sarcoid. Biopsy of a right scalene lymph node was performed and the findings were reported to be normal. Skin tests for tuberculosis and fungi were negative. In 1956 one of the tuberculin tests was positive. In sarcoid about two thirds of the patients will have a negative tuberculin test. As we progress to the 1962 admission, we note that a student heard a Grade 2 apical presystolic murmur when the patient was in the left lateral recumbent position. No other observer could confirm this. A cardiac series showed generalized cardiac enlargement, chiefly in the left atrium. There was no significant

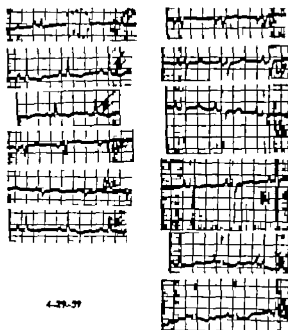


Fig 3 ECG taken in 1959 was interpreted then as showing left ventricular strain, but Dr Mauck has interpreted it as showing left atrial enlargement and nonspecific S-T T changes.

difference between the x ray study in 1952 and that in 1956 An ECG was suggestive of pulmonary disease, and the S-T and T changes were thought to be consistent with digitalis effect.

In 1959 an ECG (Fig 3) was interpreted as showing left ventricular strain associated with right atrial enlargement. I take issue with both interpretations. We observe that the broad based P wave and P mitrale are present as before, the mean QRS vector in the frontal plane remains at 80 degrees, and a sharp negative deflection is present in Lead V_1 Also observe that the R potentials in Leads V_5 and V_6 are not so prominent in these tracings as they were in 1956 and there has been a diminution in the S wave in Lead V_2. This evidence suggests that the left ventricle is becoming less prominent than it was in 1956 and one might surmise that the right ventricle is becoming more prominent. The 1962 ECG is similar

In 1963 she became more dyspneic. Pulmonary function studies revealed a marked reduction in vital capacity without evidence of airway obstructive disease. The decreased vital capacity is compatible with heart failure and pulmonary congestion The PO_2 was 60 mm Hg and I would consider this to be a low value. In this laboratory a PO_2 of 85 mm Hg is the lower limit of normal Some patients with pulmonary congestion show diminished oxygen tension but generally these patients are quite sick, usually with serious heart failure. The CO_2 tension of 39 mm Hg indicates adequate alveolar ventilation After standard exercise, the PO_2 increased to 70 and the PCO_2 declined to 34 If the alveolar ventilation is increased one might differentiate a ventilation perfusion defect from a pure diffusion defect by observing a rise instead of a fall in PO_2 I do not believe that this test is a good one. If one wishes to determine the presence of a diffusing defect I should think that one ought to obtain a carbon monoxide diffusing capacity Perhaps in the case of such a sick person it would have been more reasonable to have performed a test with the breathing of 100 per cent oxygen and then to have made measurements of arterial blood gases. Nothing in this study is incompatible with congestion of the lungs In my opinion the tests performed fail to differentiate between a diffusion defect and a ventilation perfusion problem and both could be present These studies are worth while but they do not answer the question which I assume was asked of the pulmonary function laboratory Dr Said would you comment on these findings.

DR. SAID In regard to the pulmonary function studies, such studies cannot disclose the pathology and cannot determine the etiology At best, they can indicate the location of the lesion In this case we say that the lesion was in the pulmonary capillary area and not in the airways.

DR. MAUCK The patient was started on prednisone, with some improvement in her situation I am not sure why she was started on prednisone, but probably because she was thought to have asthma or sarcoid Let us return to the physical examination and review the chest x ray films.

DR. NEAL We see a slight increase in the cardiac size. At this time the vascular markings of both hilar areas are appreciated and evidence of heart failure is present. Prominent pulmonary markings are present and the secondary interlobar fis-



Fig 4 This chest film taken in May 1964 shows evidence of pulmonary edema without appreciable pleural fluid. Left atrial and right ventricular prominence are suggested

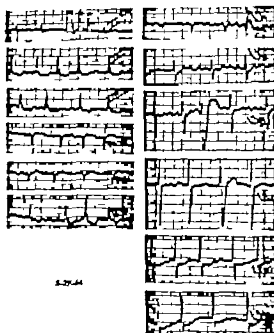


Fig 5 The ECG taken in May 1964 during the final admission indicates atrial fibrillation. Comparison with previous electrocardiograms suggests increasing right ventricular preponderance.

sure on the right has fluid within it. The chest film of 1963 shows very little change but there is further cardiac enlargement. The straightness of the left cardiac border and the slight elevation or the lack of depression of the cardiac apex both suggest changes on the right side. Films of May 1964 show more evidence of congestive failure (Fig 4) There is little evidence of pleural fluid. The prominence of the secondary fissure has decreased With barium in the esophagus, a marked displacement at the level of the left atrium was noted In the region of the right ventricle, we see fullness and opacity which suggest some left atrial and right ventricular preponderance. Intracardiac calcification was never demonstrated on films or with fluoroscopy In conclusion, our findings are those of left atrial preponderance and right ventricular preponderance. This implied some obstruction in the left side of the heart which produced congestive failure and cardiomegaly in this patient From the x-ray films alone (with the broad impression on the barium filled esophagus, by the enlarged left atrium) one might think seriously of combined mitral stenosis and insufficiency

DR MAUCK From the standpoint of the cardiologist, we prefer to make a diagnosis of the specific valvular lesions on the basis of the physical examination. I frequently have seen pure mitral stenosis in which there was some x ray evidence of left ventricular hypertrophy or enlargement I wonder whether when the right ventricle is extremely large, the left ventricle is not simply pushed posteriorly and this positional variation gives the impression of left ventricular enlargement. I am certain that I have seen this situation and do not believe that we need to have a mixed lesion to explain these radiologic findings.

The last electrocardiogram (Fig 5) was taken during the patient's final hospitalization Atrial fibrillation has appeared There is now an S wave in Lead I Since the last ECG the mean QRS vector in the frontal plane has moved to the right. This significant shift indicates the presence of increasing right ventricular preponderance. The S waves in the right precordial leads have become less prominent, and the R

wave in Lead V_1 is slightly less prominent than it was before.

On cardiac catheterization the mean wedge pressure was 27 mm Hg (approximately twice normal) This indicates that pulmonary venous and capillary pressures are high as if from failure of the left ventricle, mitral block with elevation of atrial pressure, or obstruction in the pulmonary veins. The pulmonary arterial pressure was extremely high 112/54 mm Hg Thus, the pulmonary vascular resistance has increased If one simply takes the mean pulmonary arterial pressure, subtracts the mean wedge pressure from it and divides it by the cardiac output he will obtain the pulmonary vascular resistance. There is a marked elevation in this patient which indicates restriction of flow in the lung itself perhaps due to pulmonary arterial spasm or organic change such as intimal thickening and fibrosis, medial hypertrophy or possibly recurrent pulmonary emboli. The end-diastolic pressure in the right ventricle is 17 which is markedly elevated and indicates that the right side of the heart was failing The right atrial mean pressure is elevated to 13 This demonstrates that the right ventricle is involved in addition to the pulmonary veins and capillaries. By x ray the left ventricle is not much enlarged if at all When we relate this to the physical examination with the loud first heart sound accentuated pulmonic second sound and a shift of the ECG vector toward the right the diagnosis of the mitral block is apparent. An obstruction exists at the left atrioventricular valve. What could produce this?

In the differential diagnosis of mitral block certain lesions are obvious and must be ruled out Among the rare lesions would be cor triatriatum or some primary obstruction of the pulmonary veins. Both of these are congenital anomalies which are noticeable in youth Characteristically they do not distort the first heart sound since there is no gradient over the A V valve. Cor triatriatum is generally associated with a systolic murmur in the third and fourth left intercostal spaces and occasionally with a diastolic murmur These are not very likely Lutembacher's syndrome (mitral stenosis with an atrial septal defect) should be considered This situation does not characteristically produce enlargement of the left atrium since there is a shunt from the left to the right atrium This diagnosis was not supported by the cardiac catheterization data which showed a right atrial oxygen saturation of 40 per cent. The possibility arises that the block is a left atrial myxoma. The best means of making this diagnosis would be left atrial cardioangiography and demonstration of a filling defect in the left atrium This entity may be associated with changing heart murmurs at the apex It sometimes is associated with a systolic and a diastolic murmur and at times is not associated with a murmur Patients frequently have systemic manifestations of a left atrial myxoma including fever anemia elevation of sedimentation rate, and an elevation of the serum globulin Since none of these were present I rule out left atrial myxoma

To me, this case is perfectly compatible with rheumatic heart disease, and I shall make a diagnosis of mitral stenosis as the dominant lesion The 20-year history of increasing symptoms are compatible with this diagnosis, and all of the clinical findings along the course fall into the disease spectrum The absence of a diastolic murmur and the lack of an opening snap were probably due to low cardiac output. Atrial thrombosis is very frequently observed in this situation Recently cases have been reported emphasizing the absence of a diastolic murmur in the face of a low cardiac output and atrial fibrillation.

The sudden death of this patient while she was getting up to use the bedpan suggests four possible complications of the disease. Digitalis intoxication is the least of the possibilities. Second the possibility of an embolus to the lungs from the lower extremities or right heart is a consideration Dr Paul Wood has stated that this is the most frequent cause of death in patients with chronic mitral stenosis. Third an atrial thrombosis may occlude the mitral valve orifice and produce sudden death This is the most probable explanation Finally emboli from the left atrium occur frequently and may involve any organ We shall find changes in the lungs and pulmonary arterioles at postmortem I

think that we shall find atrial thrombi occluding the mitral valve orifice

Clinical diagnosis (1) Mitral stenosis (2) Boeck's sarcoid with cardiac involvement (?) (3) pulmonary embolus.

Dr Mauck's diagnosis (1) Rheumatic heart disease (2) mitral stenosis (3) occlusion of mitral orifice by thrombus.

Pathologic discussion

DR. GOODALE I would first like to congratulate Dr Mauck on his excellent discussion of the differential diagnosis in this case. The most valuable part of any clinical pathologic conference is the discussion correct clinical diagnosis is of secondary importance. In this particular case Dr Mauck has combined the two

This patient's troubles all were related to rheumatic heart disease. The heart was hypertrophied weighing 440 grams. The left ventricle was of normal thickness the right ventricle was twice normal thickness. The mitral valve was severely stenotic. It had a typical "fish mouth" appearance and would admit only the tip of the little finger Marked distortion of the mitral valve by the thickened shortened chordae tendineae and by fibrosis and calcification of the leaflets was evident.

The left atrium was dilated to approximately five times normal size. In the atrial appendage was a thrombus, to which was attached by a thin stalk, a large ball (Fig 6) of thrombus that at autopsy lay directly over the stenotic mitral valve. I believe that the immediate cause of death in this patient was occlusion of the mitral valve by the thrombus.

All valves other than the mitral were normal. The coronary arteries showed no atherosclerotic change yet in the myocardium of the left ventricle was a large area of grayish tissue representing a healed infarct Although we could not demonstrate the actual occlusion it is most likely that an embolus to the coronary artery from the left atrial thrombus was the cause of the infarct We found no fresh occlusions in the coronary vessels to suggest this mechanism as the immediate cause of death Microscopically the atrial thrombus showed advanced organization where it lay adjacent to the endocardium so that it had been present for at least several weeks.



Fig 6 A large thrombus hangs into the dilated left atrium At autopsy it sat upon the deformed, scarred stenotic mitral valve It is joined by a pedicle of thrombus to a mass of the same material in the atrial appendage

The myocardial infarct contained hemosiderin pigment and was composed of fibrous tissue which was not mature It was approximately 4 to 6 weeks old No Aschoff bodies or alterations of subendocardial ground substance were present to suggest activity of the rheumatic process.

The lungs were heavy weighing three times normal (1 700 grams) They were markedly edematous and the cut surface showed the diffuse brownish tinge so often seen with long-standing mitral stenosis. Microscopically the arterioles presented severe fibrous intimal thickening This form of arteriosclerosis is commonly seen in pulmonary arterioles which have been subjected to years of hypertension but it is not possible to correlate closely the degree of fibrous intimal thickening with the length or severity of the pulmonary hypertension [1]

Microscopically the alveoli contained numerous hemosiderin-filled macrophages. Many alveolar walls were thickened by fibrous tissue. These two findings account for the classic brown induration seen grossly The fibrosis of the alveolar walls is also responsible for diminished oxygenation and for increased pulmonary capillary pressures The patient had a history of

bronchial asthma and there are mild pulmonary changes to substantiate that diagnosis bronchiolar lining cells loaded with mucus, hyalinization of the basement membrane, and a peribronchial chronic inflammatory cell infiltrate that included eosinophils. It is doubtful that these changes were severe enough to produce symptoms.

A diagnosis of thyrotoxicosis had been made some years previous to death. At autopsy only the left lobe of the thyroid remained it was very small weighing 12 grams and was microscopically normal

Pathologic diagnosis (1) Rheumatic heart disease, inactive with (a) mitral stenosis, severe, and (b) left atrial dilatation, marked with ball valve thrombus formation

REFERENCE

1 Goodale F., Jr et al. Correlation of pulmonary arteriolar resistance with pulmonary vascular changes in patients with mitral stenosis before and after valvulotomy New England J Med. 252:979 1955

The mechanism of flutter and fibrillation*

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A re-evaluation of the various theories of the mechanism of flutter and fibrillation seems to be appropriate because several recent contradictory reports require critical review.

One hundred and fifteen years ago it was noted that application of an electrical current to the ventricles of the frog heart causes cessation of the coordinated contractions and provokes the dissociated movements which we know as fibrillation. In spite of the ease with which this phenomenon can be provoked its mechanism in man remains uncertain. This also applies to flutter which was discovered much later. We are best informed about the mechanism of atrial flutter and the discussion of this arrhythmia will therefore be presented first.

Atrial flutter

More than 60 years ago it was suggested that flutter is caused by rapid firing of impulses in a center. Already in 1895 Engelmann postulated the activity of multiple foci in atrial fibrillation. The theory of re-entry was advanced when it was demonstrated that an excitation wave may circulate for hours in the ring muscle of the mollusk, in rings cut from the turtle heart and even in suitably arranged nerve-muscle preparations. Lewis attempted to demonstrate this mechanism in the dog in atrial flutter after faradic stimulation and concluded that in this arrhythmia an excitation wave usually travels around the venae cavae up or down the taenia terminalis. The re-entry theory was widely accepted in spite of serious objections raised early[22] and experiments which invalidated this theory. In the heart of the dog in situ atrial flutter was created by faradic stimulation. Broad ligatures were applied across the taenia terminalis compressing not only this structure but also other muscle bundles which could conceivably be used as a pathway for a re-entry wave. These ligatures failed to stop or alter the existing flutter. Application of additional ligatures was also ineffective.[23]

It was also shown that the flutter waves closely resembled the P waves of the sinus or A-V rhythm preceding or following it. When the form of the P waves was altered by compression of muscle bundles or ligation of atrial arteries the flutter waves changed in the same manner.[23] These results were confirmed.[7] Such findings are not compatible with the theory that atrial flutter is based on the continuous circulation of a central wave around the venae cavae from which the impulses spread radially to the rest of the atria. They suggest that a center is firing rapid impulses. A few observations in man are available which corroborate these experimental find

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*Although the data upon which this article is based were obtained from animals other than man, they deal with fundamental problems in clinical cardiology. This article presents information which could not be obtained on man but which is applicable to man.

ings. In these cases the rhythm changed often from sinus rhythm to A-V nodal rhythm and back; flutter in short paroxysms appeared. The flutter waves sometimes resembled the positive P waves, and sometimes, when flutter followed or was preceded by A-V rhythm, they were inverted in Leads II and III like the P waves of the A-V beats.[37,41,43]

Prolonged atrial flutter provoked by faradic stimulation of the dog heart is not easily obtained. In many hearts, only atrial fibrillation appears, and in others the flutter is too transient to permit study. In 1947 Rosenblueth and Garcia Ramos[39] recommended a new method to create persistent experimental flutter. The authors demonstrated that the crushing of an atrial segment between the venae cavae followed by faradic stimulation leads to prolonged atrial flutter. The authors assumed that an obstacle is thus created enabling the circus wave to move around it. It should be emphasized, however, that no anatomic proof has been given for the presence of a circular muscular pathway around the venae cavae or the crushed area. However, the ease with which persistent electrical flutter could now be produced, as well as other data to be discussed below, helped to revive the re-entry theory.

As Lewis had done before them, the authors attempted by means of direct leads to map out the path of the circus wave and claimed to have shown the presence of a re-entry mechanism.[40] Their method was criticized because the use of bipolar leads does not permit differentiation between intrinsic and extrinsic effects.[23] Other investigators using an improved technique actually found in similar experiments a spread of the excitation wave suggesting the presence of an ectopic focus firing off stimuli.[21]

In electrically induced flutter, faradic vagal stimulation usually increases the rate of flutter. Unless one postulates that during vagal stimulation atrial conduction is faster, the increase in rate cannot be explained by the re-entry theory. The path around the obstacle cannot become shorter and the assumption that this path becomes more straight, and therefore shorter, has no factual basis.

Another strong argument against the presence of a circus wave is the result of the following experiment. Flutter was established by crushing and faradic stimulation of the atria of the exposed heart of the dog. A ligature was then applied across the crushed segment encompassing all muscular bands on both sides, reaching far out into the smooth portions of the atria on one side and close to the A-V border on the other. The flutter persisted unchanged.[33] The creation of prolonged flutter after crushing can be explained by the fact that this procedure damages specialized sinus node fibers and alters them in such a way that faradic stimulation creates more readily centers of rapid firing. For this explanation speaks the result of 11 experiments in which we crushed with a hemostat a strip of the left atrium and thus created an "obstacle" there for the circulation of a re-entry wave. Only in one experiment was faradic stimulation followed by prolonged atrial flutter. Different results should be expected if only creation of an obstacle were needed in order to obtain prolonged flutter after faradic stimulation.

In 1947 it was shown that focal application of aconitine on any part of the atria, even on the tip of the left atrial appendix, created flutter of long duration.[34] Cooling or clamping off the focus of application stopped the flutter at once. This indicated that the arrhythmia originated in the treated area. Delphinine acts in the same manner. This alkaloid, which is related to aconitine, induces flutter and rarely fibrillation and therefore serves better for such experiments.[40]

In aconitine-induced or delphinine-induced flutter, pressure exerted on the focus of application with the small head of a probe increased the rate of flutter or changed it into fibrillation.[46,47] This result demonstrated that this type of flutter is caused by the rapid firing of impulses in a focus.

In an attempt to reconcile the aconitine flutter to the circus movement theory some authors have proposed that aconitine focally applied creates an obstacle and thus a "focal" circus movement is made possible which would have the same general effect as a rapidly firing focus.[7,31,38] In

order to obtain a circus motion in a muscular ring certain conditions must prevail There should of course be a closed circular muscular pathway This must have a certain length and the single fibers must have a refractory phase of a certain duration. Finally the speed of conduction must be such that the head of the circulating wave does not meet its tail However flutter or fibrillation is created every time either aconitine or delphinine is applied focally Obviously all the requirements cannot be fulfilled each time so as to make a circus movement possible. Furthermore the flutter obtained by crushing and faradization has a rate of about 480 per minute with a pathway of about 9 cm.[36] If the pathway were only a few millimeters in length the rate of flutter would be several thousand

High-speed cinematography[17] did not help in the controversy A circus wave in a small bundle need not cause visible contractions recordable by motion pictures. What we do see are contractions of the appendix or atrial muscle mass which proceed from the base to the apex according to both theories.

Several authors claim that two forms of flutter exist. One is the "rapid focus flutter caused by aconitine and delphinine and the other is the "circus movement flutter which is represented by the electrical flutter with or without crushing The assumption of the existence of these two forms is based on experiments in which fundamental differences in the response of each type to various influences were observed

Atrial flutter caused by aconitine was said to disappear gradually after administration of procaine amide, whereas it stops abruptly when caused by electrical stimulation However the authors describe 5 experiments out of 29 in which aconitine flutter stopped suddenly and in another report marked slowing of the electrical flutter was found before reversion to sinus rhythm under the influence of quinidine. The response to vagal stimulation is identical in both types of flutter and the statement that the influence of acetylcholine on electrical flutter is different from that on aconitine flutter[19] is at variance with this fact.

It is true that aconitine flutter reappears after having been abolished by procaine amide or quinidine whereas electrical flutter does not. This, however does not indicate a fundamental difference in mechanism Once the aconitine focus has been created it persists for one hour or more, and when the effect of the antiarrhythmic drug on excitability and conduction of the atrial muscle wears off the persistent aconitine focus will re-establish the tachycardia. On the other hand it is clear that, once the center of rapid formation of impulses created by electrical stimulation has been suppressed by quinidine or procaine amide it will remain inactive until this or another center are reactivated by restimulation. Similarly the prompt interruption of the aconitine flutter by focal cooling is explained by the influence of the cold thermode on the center directly Electrical flutter often fails to respond to focal cooling because the exact location of the center is unknown This type of flutter may originate in any specialized fiber of the sinus node or A-V node. We shall see later that flutter or fibrillation provoked by electrical stimulation or acetylcholine is always promptly stopped by simultaneous cooling of these two structures. Stretching accelerates aconitine flutter[44] whereas electrical flutter responds differently[4] However in the aconitine flutter we know where pressure and stretch should be exerted whereas in electrical flutter we do not. The obvious explanation of an acceleration of the heart on cooling found by one investigator is that the pressure exerted by the cooling thermode near and not at the focus provoked an increase in the rate of formation of impulses.

Lanari and his co-workers[19] compared by means of direct leads from the atria the flutter caused by crushing and electrical stimulation with the flutter due to aconitine As expected the impulse was found to spread radially from the aconitine focus, whereas in electrical flutter it moved around the obstacle created by the crushing However the authors did not study the pathway of the excitation wave in aconitine flutter after crushing the same area as in electrical flutter It would seem to us that, regardless of the focus of origin the creation of an obstacle, such as a

crushed area, would force the excitation wave to move around it in an incomplete circle.

More arguments for the ectopic focus mechanism

Recent experiments[11,44] have shown that focally applied aconitine causes the appearance of local after potentials. When they reach a certain threshold *impulses* are fired These after potentials appear in the common myocardial fibers only after a conducted impulse excites them Therefore if aconitine *has been applied to the* appendix of an atrium and this is clamped off the flutter will appear only when this portion is again stimulated The same result has been obtained with barium[2] and in the clamped-off appendix treated with acetylcholine. It fibrillates immediately when it is stimulated once.[41]

It is important to note that in order to achieve flutter after crushing the rate of electrical stimulation must be between 500 and 600[18] Burn[8] found that the atria of a perfused dog heart under the influence of acetylcholine must be stimulated 750 times per minute in order to produce fibrillation Rapid stimulation increases the negative after potential[1,23,44] and this may lead to rapid firing in a center in the sinus or the A V node. This assumption is supported by the finding that experimental flutter appears in two forms. In the first *the F waves are positive, similar to the* P waves seen normally in Leads II III and aV_F whereas in the other the F waves are negative in these leads and resemble the P waves in A V rhythm The same two forms are seen in clinical flutter the latter *much more often than the former* Even in the same experiment and in the same patient (*see above*) both forms may be found at different times.

The spread of the excitation was found to be clockwise or counterclockwise around an obstacle in these two forms, and this has been quoted in support of the circus *movement theory*[30] *However it is more* likely to assume that in one form the flutter is caused by a focus in the sinus node and in the other form by a focus in *the A V node Since the flutter waves are* caused by the activation of the mass of the atria and not by the small re-entry wave it would be strange that the majority of the clinical cases would have atrial vectors similar to those seen in A V rhythm unless we assume that they originate in that area

If the sinus node is clamped off and flutter or fibrillation appears after focal application of acetylcholine, cooling of the A V node terminates it promptly It reappears at once when the cooling is stopped[33] Garrey's observation that fibrillation persists in each part after separation of the atria by cutting or compression into *different parts*[14] *has been used as an argu*ment against both rapid impulse formation and circus movement.[14,30] Similar observations on the fibrillating ventricle have been reported before (Kronecker *Hering*) The simultaneous flutter of one atrium during fibrillation of the other has also been interpreted as speaking for a circus mechanism[44] This, however is not justified since it is established that under certain conditions one atrium may receive its impulses from the sinus node and the other from the A V node[42]

Two experimental findings have been reported[30] which if confirmed would favor the presence of a re-entry mechanism in flutter One is the observation that prolongation of the obstacle by additional crushing slows down the rate of flutter The assumption is that the circulation wave is forced into a longer pathway *Actually Rytand attempted to show in* clinical studies that the rate of flutter is slower in patients with larger right atria[33] However Kimura and associates[15] found that there is not always a slowing of the rate when the pathway becomes larger *Even with considerable lengthening* of the path the rate was sometimes unchanged The second argument presented as speaking in favor of the re-entry mechanism is *the reported observation that flutter* stops when the obstacle created by crushing is extended downward to the A V border thus interrupting the pathway In 13 *unpublished experiments we noted* that, after crushing an area of the right atrium extending from the inflow of the vena cava superior to the A V border we were still *able to induce persistent fibrillation* by faradic stimulation However we had the impression that the attacks did not last

long. This problem requires further investigation.

On the basis of the available data it must be concluded that experimental flutter can be caused by the rapid formation of impulses, whereas the theory of re-entry still requires proof. There is no definite proof for either mechanism in clinical flutter.

Comparison between atrial flutter and atrial paroxysmal tachycardia

The clinical as well as the electrocardiographic differentiation between these two disturbances of rhythm may be difficult, particularly in the case of atrial tachycardias provoked by digitalis. The rate and the configuration of the atrial waves may not be characteristic for either disturbance. The only definite difference is the fact that vagal reflexes stop a large percentage of atrial paroxysmal tachycardias, whereas in clinical atrial flutter these reflexes remain ineffectual. In the experiment, faradic stimulation of the vagus usually increases the rate of flutter and often transforms the flutter into fibrillation. Sometimes the experimental flutter stops shortly *after* electrical stimulation of the vagus; this may be caused by the prolongation of the refractory period observed at this time ("rebound effect").[11]

Clinically, paroxysmal atrial tachycardia is commonly found in the absence of heart disease, whereas in the case of flutter heart disease is often present. The response of these two conditions to therapy is quite different. Flutter is often converted into fibrillation by digitalis. This is not usually observed with a paroxysmal atrial tachycardia.

In this connection observations on the changes in rhythm after focal application of a few crystals of delphinine on the atria are relevant.[44] After an interval of 5 to 10 minutes following the application of the delphinine to a point on the appendix of the right or left atrium the heart rate slowly increases. Vagal stimulation slows and stops the heart, and after cessation of the stimulation the rate gradually increases and reaches the same level as before the stimulation. This is the response of a sinus tachycardia. A few seconds or a minute later, the rate becomes much faster. Vagal stimulation stops the tachycardia suddenly without previous slowing of the rate; after the end of vagal stimulation the tachycardia recurs suddenly with the full rate as before the stimulation, just as in a paroxysmal tachycardia. Finally, often without any changes in rate and form of the P waves, vagal stimulation leads to an increase in the atrial rate, a response which is typical for flutter. The changes in the center which cause the sudden change of response to vagal stimulation are unknown.

On the basis of all available data, paroxysmal atrial tachycardia and flutter should be separated.

Atrial fibrillation

Experimental flutter is readily transformed into fibrillation by measures which increase the rate of flutter. Thus mechanical irritation of the area on which aconitine or delphinine has been applied, such as pressure with a probe or stretching[44, 7] or faradic stimulation of the vagus or sympathetic nerves,[44] will lead to atrial fibrillation if the atrial rate increases to a critical level.

Theoretically, the rapid formation of impulses in a center may create fibrillation in two ways. The first way would be that the rate increases to a level at which the impulses formed in the center are not able to spread uniformly over the atria. Islands of refractory tissue appear, leading to an irregular pattern of conduction. The fact that cooling of the area on which the above-named alkaloids have been applied stops the fibrillation at once, occasionally after converting it at first to flutter, and the finding that the cessation of the cooling leads to a reappearance of fibrillation, sometimes after a short run of flutter, cannot, in our opinion, be explained by another mechanism.[44, 45-47]

Atrial fibrillation caused by acetylcholine locally applied or by electrical stimulation of the atria,[49] or aconitine fibrillation persisting for a while[44] disappears only if both the sinus node and the A-V node are cooled simultaneously. This demonstrates another way in which the formation of impulses in a center can create fibrillation, namely, the presence of more than one center. We consider it to be probable that the rapid

firing of impulses when it reaches a certain rate, induces other specialized fibers to form impulses rapidly just as nerves, ganglia or cortical centers show an after discharge after rapid stimulation.[1,2,20,21]

The increase in the negative after potential by rapid stimulation has been mentioned above. When a negative after potential reaches a certain magnitude spontaneous firing of impulses is observed in nerve and heart muscle. This second mechanism is still hypothetical but it has been shown in the heart muscle that rapid stimulation leads to the firing of impulses with a rapid rate.[2,24] The question whether flutter and fibrillation are due to the same mechanism has frequently been discussed. It appears that this is the case with two differences between the arrhythmias. One reason is the higher rate in fibrillation and the other is the fact that in fibrillation more than one center may exist. The electrocardiogram in unifocal fibrillation is identical to the one in fibrillation in which more than one center is present.

The argument has frequently been put forward that it does not seem to be possible for one center to continue the rapid firing for many years. It is known however that the heart rate in some mammals under physiologic conditions may approach 1,000 beats per minute and it is even greater in some birds.

It has been stated that fibrillation cannot appear in heart muscle portions not containing specialized fibers.[22] Since fibrillation can be provoked by the application of aconitine on the tip of the appendices of the right and left atrium where the presence of specialized fibers is unlikely this statement is probably incorrect. In fact recent investigations revealed that non pacemaking common muscle fibers are, under certain conditions capable of firing rapid impulses provided that they are depolarized and develop after potentials.[44] This has been known for a long time from the study of nerves.[21]

Unfortunately those who are partial to one theory of the mechanism of these arrhythmias tend to neglect and discard data speaking against it.

In conclusion it may be said that there is evidence that fibrillation can be caused by the rapid firing of impulses in one or more foci. The occurrence of fibrillation as a consequence of a re-entry mechanism alone is a fascinating hypothesis. Re-entry waves do occur and their appearance is facilitated by longer refractory periods and delayed conduction.[22] However they may be the consequence of the rapid firing of impulses rather than the primary mechanism.[14]

Ventricular flutter and fibrillation

The mechanism of ventricular fibrillation is unknown. Lewis was well aware of the difficulty of extending the circus movement theory to fibrillation of the ventricle. The presence of several circus pathways and different wave fronts has been assumed but again we are dealing with hypothetical assumptions.

Ventricular fibrillation cannot be elicited in small ventricular sections. This does not prove a re-entry mechanism. It may mean that the muscle portion is too small to permit several centers to form impulses or to permit irregular conduction and block areas.

As was stated above topical aconitine will cause a ventricular tachycardia or flutter and later fibrillation. As long as no fibrillation is present cooling stops the tachycardias, but it is ineffective as soon as fibrillation supervenes.[41]

Just prior to the onset of ventricular fibrillation in the experiment and often in clinical observations, several ectopic beats appear resembling each other and occurring with increasing rate up to 600 per minute suddenly fibrillation sets in.[21,42] This indicates that at least the initial phase is one of ectopic impulse formation suddenly followed by another mechanism.[25] Similar observations were made in the initial and final stages of atrial fibrillation. Re-entrant waves could be excluded. Oscillating negative after potentials were observed.[41] Whereas many authors believe that the rapid rate makes a re-entry mechanism possible by creating block and abnormal conduction we consider the possibility that the rapid formation of impulses increases the negative after potential and this leads to firing in myocardial cells.

The experience that one stimulus mechanical electrical or natural (in the form

of an extrasystole) arriving during the vulnerable phase may throw the heart into fibrillation has often been quoted as speaking in favor of a re-entry mechanism since an early impulse will meet refractory tissue and will move around it in a circuitous path. Although this is a formidable argument, one should not forget that in nerve and heart muscle under conditions precluding a circus movement[9] it has been found that excitation by a conducted impulse arriving in an altered area may lead there to the firing of impulses at a rapid rate. The provocation of attacks of A-V nodal tachycardia by very early atrial extrasystoles[47] is an instance of rapid firing of impulses under conditions ruling out a re-entry mechanism.

One argument against the explanation of fibrillation by the assumption of the activity of several centers is the fact that ventricular fibrillation may end suddenly without any visible change in the electrocardiogram. It is difficult to assume that all active centers stop firing at the same time. We do know, however, that atrial fibrillation caused by the activity of one center resembles that caused by the activity of more than one, and the same assumption may be valid for the ventricular variant. When the last of several centers stops firing, ventricular fibrillation ceases.

Were a re-entry mechanism responsible, the head of the single or multiple re-entry waves should have excitable tissue in front of them. Otherwise a re-entry is impossible. A strong electrical shock depolarizes the whole heart and should terminate the fibrillation immediately. Actually, one does not succeed in all instances and often several shocks are necessary. Thus Oram[31] in 129 episodes of atrial fibrillation needed for conversion into sinus rhythm more than one shock 62 times.

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Appraisal and reappraisal of cardiac therapy

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Antianginal drugs
Part I The therapeutic role of coronary vasodilators

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The therapeutic indications for and the clinical role of drugs considered to be coronary vasodilators are quite uncertain and a source of considerable confusion to the clinician It seems to be appropriate, therefore, to begin a series of appraisals of specific antianginal agents, with a consideration of what the goals of therapy and what the guidelines to efficacy of these drugs should be.

Therapeutic goals The treatment of coronary atherosclerosis can be subdivided into the following (1) the asymptomatic stage (suspected electrocardiographically or angiographically) (2) the anginal stage, (3) the prodromal stage of myocardial infarction, (4) the stage of myocardial infarction, and (5) the postmyocardial infarction stage By either implication or extrapolation the use of coronary vasodilators has been suggested in the treatment of each of these stages. No proof exists to indicate that *in man* these drugs are of value in any of these stages, with the possible exception of the anginal stage.

It has been suggested that they are useful at any stage of arteriosclerotic heart disease because of their questionable ability to promote the development of collateral circulation. The fact is that proof of this proposed action does not exist *for man*. Moreover even if such collateralization is mediated by these drugs, it remains to be proved that it is of such order of magnitude as to improve angina pectoris, prevent or delay the development of subsequent myocardial infarctions, or affect prognosis. All therapeutic objectives that can be proposed for these drugs can be compressed into these two (1) amelioration of angina pectoris and (2) prevention of myocardial infarction.

No proof exists that the second objective can be achieved by the use of coronary vasodilators, since the long term controlled experiment with a large series of patients required to validate this point has not been conducted Ultimately we are left, therefore with an evaluation of the potential value of these drugs in the treatment of angina pectoris.

In the treatment of angina pectoris the following secondary goals can be proposed (a) the drug is given to treat the acute attack with anticipated diminution in duration and intensity of the pain or (b) the drug is given prophylactically to (1) decrease the frequency of attacks or (2) improve work capacity even though angina eventually supervenes.

Evaluation of efficacy Once these goals are clarified it becomes essential to determine the usefulness of these drugs for each of these three last-mentioned goals by carefully conducted experiments. It is here that most of the difficulties have arisen. Angina is a syndrome and as such cannot be measured objectively The so-

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called *objective methods* such as coronary cineangiography electrocardiography radioisotopic transcoronary and coronary sinus catheterization blood flow measurements suffer from the inherent defect of not being able to measure angina They may be useful in elucidating mechanisms of action if it can be proved that these drugs do affect angina pectoris.

The *subjective methods* which are most applicable to the problem suffer from the great inherent defects of subjectivity but unfortunately are essential to the clinical assay of these agents. Two subjective methods are available In the first method the rate of spontaneous anginal attacks, the consumption of nitroglycerin and some estimation of work performance are recorded daily by the patient on data sheets as he receives the drugs Whether the study is conducted in an uncontrolled manner or by the more desirable double-blind design it is most important that close attention be paid to the selection of subjects. These subjects should approximate those who would merit therapy clinically by virtue of such frequency of cardiac pain as proves to be incapacitating It is fairly obvious that a patient who has an attack of angina per week or per month is hardly a suitable candidate for a study in which the drug will be administered over a few weeks and compared with a like period of administration of placebo That such studies should be double blind can hardly be questioned some series report an incidence of placebo reactors as high as 60 per cent among angina patients. It is quite possible that most of the discrepancies among various reports using this method or its modifications arise from the selection of subjects. Indeed angina pectoris of a degree and constancy suitable for clinical study is relatively rare Recurrent angina is present in about 10 per cent of patients with arteriosclerotic heart disease. Significant angina that is at least one attack of pain per day is found in about 2 per cent of such patients Thus it has been difficult to obtain enough suitable subjects on whom to conduct good double-blind studies, and many of the discrepancies reported in print are due either to small series not suitable for valid statistical analysis or to poor selection of patients. This method of study has other drawbacks, the chief of which are the reliability of the patient in making daily entries and in taking the drug daily

Another type of subjective assay of antianginal drugs is a quantitative method requiring performance of an exercise tolerance test to the *point of angina* under controlled laboratory conditions. This is certainly the most refined method of bioassay that we possess for the study of the efficacy of these agents in angina of effort In the original test the environmental temperature was lowered to 45-55°F which unfortunately introduced an additional experimental factor For the pure evaluation of the prophylactic value of these drugs on angina of effort, room temperature has been employed This tolerance method of study determines not only pre-anginal work capacity but also the duration of the ensuing attack. In the reviews of specific drugs that will follow great emphasis will be placed on the results obtained by this type of human assay in deciding the clinical usefulness of these drugs.

Finally the confusion that has prevailed in this field has arisen not only from lack of definition of therapeutic goals but also from the inaccurate use of terminology It is best not to use interchangeably such terms as coronary insufficiency myocardial anoxia diminished coronary blood flow angina pectoris, and others Doing so has in itself led to confusion of the therapeutic goals of these drugs. Furthermore animal experimentation is irrelevant to therapeutic applicability for laboratory animals do not suffer from angina pectoris nor do they sustain spontaneous myocardial infarction analogous to the clinical situation There has been a recent awareness that the relief of angina pectoris may not depend on coronary vasodilation Moreover other drugs which are not vasodilators have been proposed for the treatment of angina From all these considerations and because the therapeutic use of these agents has been narrowed to the treatment of angina pectoris these drugs are best designated as antianginal agents, and their clinical usefulness should depend on their specific antianginal efficacy

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Experiences with implanted cardiac pacemakers

The use of long-term electrical stimulation of the heart to prevent syncope or other circulatory failure caused by heart block has become well established. In specific instances uncertainty will continue as to how many syncopal attacks should be permitted before resorting to pacemaker implantation. For example, one group has followed without operation certain patients with chronic heart block who have had "unequivocal episodes of unconsciousness . . . not sufficiently frequent or severe to justify operation in the consultant's opinion."[?] With increasing evidence of the safety of the operation required for implantation, there has been increasing willingness to use it. Multiple factors, which tend to prohibit generalizations about the need for artificial pacing, are involved. These include ( ) great variability in the natural history of heart block, (b) the probability of serious, coexistent disease in a group of often elderly patients, tending either to lessen the benefits or to increase the urgency of a normal pulse rate, (c) the morbidity and mortality resulting directly from the use of the pacemaker, (d) the reliability of the instrument in performing its function, and (e) the multiplicity of techniques and the continuing evolution of instruments for this purpose. From such a complex set of variables, however, some principles on which to act must be periodically extracted and revised. This requires the collection of experiences in large numbers of patients. In this report our experience is added to those of others already published, in an effort to characterize further the current state of this problem. This discussion will be confined to problems of long-term pacing only.

At the University of Virginia Hospital 18 patients have undergone implantation of pacemakers. These patients have been followed for periods of from 1 month to 4 years after operation, with an average follow-up period of about 1 year. All except 3 were older than 60 years at the time of operation. The A-V block in one patient appeared after replacement of the aortic valve. In the others the etiology was unknown or presumed to be arteriosclerotic heart disease. In none of these patients was a history of definite prior myocardial infarction obtained. The preoperative QRS complexes in the electrocardiogram were normal in 5, showed a right bundle branch block pattern in 6, left bundle branch block in 4, and alternated between right and left bundle branch block in 3. In 2 of these patients the atrioventricular block was paroxysmal, and the cause of their syncope was documented only by frequent electrocardiographic monitoring. The duration of syncopal attacks prior to implantation ranged up to 8 years in two instances.

The technique of operation was the usual thoracic and abdominal-wall approach[1] in all but one instance. One patient, aged 69, had severe generalized rheumatoid arthritis and restricted thoracic motion. The electrodes were applied via a median sternotomy to the right ventricle instead of using a left thoracotomy in this patient, in order to preserve both pleural spaces. The instrument used was a constant-rate pacemaker in 16 patients[4] and a P-wave synchronous pacemaker[5] in the 2 patients with intermittent block.

All of these patients survived the operation and have benefited from the provision of artificial pacing. One elderly diabetic patient died a year later of a cerebral artery thrombosis; her pacemaker was functioning normally at the time. All of the other patients are alive and, with one possible exception, free of symptoms related to heart block. The problem of recurrent syncope seen in 3 patients will be described in greater detail subsequently. In each instance of recurrent syncope the cause has been corrected for periods of more than a year after its occurrence. The other complications have included *two instances of an early rise in stimulus threshold*, one postpericardiotomy syndrome, one paralyzed left hemidiaphragm, and one transient serous effusion around the battery unit. There has been return of atrioventricular conduction in 4 patients, all of whom appeared preoperatively to have permanent complete atrioventricular block. It is evident from these results that the implantation of a cardiac pacemaker is a relatively safe operation if the usual precautions in regard to the use of catheter or external pacing during anesthesia are followed. The complications described constitute a moderately frequent problem. Although no major morbidity resulted from these complications, they are noteworthy accompaniments of this relatively new surgical area. Syncope has recurred for different reasons in 3 of these 18 patients, in each instance after a year or more of uncomplicated pacing. One instance was due to electrode breakage in 1962; this problem has probably been eliminated by subsequent improvements in electrode design. Insertion of a new power unit when component failure occurred in 2 patients has restored pacing. An entire new unit, including electrodes, was required even-

tually in the patient with a broken electrode. A higher incidence of recurrent syncope in the earlier patients suggests that recurrent syncope will become more frequent as more of these patients are observed for longer periods of time.

Battery depletion is certain eventually with the present types of power source. It remains to be seen whether battery depletion can be successfully anticipated and treated prior to recurrent syncope. An interesting problem has been ventricular tachycardia in one of the 4 patients who showed a return of normal A-V conduction after implantation of pacemakers for apparently permanent complete heart block. In general, the return of A-V conduction after pacemaker implantation has been reported to be moderately frequent and benign. The ventricular tachycardia in this patient could not be shown to result from pacemaker stimuli as has been noted occasionally by others. It occurred during normal A-V conduction at an adequate pulse rate and appeared to be independent of the pacemaker. Treatment has consisted of the administration of procaine amide orally, which has been employed in similar situations by Chardack.[3] Nevertheless, as the probability of battery depletion increases with time, the safety of having such a patient on a suppressive drug diminishes because of his possible dependence upon an idioventricular rhythm after cessation of pacing.

A more meaningful picture of the over-all experience with implanted pacemakers can be obtained by adding our results to those in several of the larger series in the literature.[2-4,9] This review is not intended to be complete, since only those reports in which the analyses included the numbers of patients having fatal and nonfatal instrumental difficulties were considered. These are also short-term analyses in which the average time after implantation was from 1 to 3 years. A total of 292 patients was given implantable pacemakers of sufficiently similar electronic properties to permit this grouping. There were 43 deaths from all causes (15 per cent) during the period of observation. There were 10 deaths (3 per cent) due either to recurrent asystole or to infection around the pacemaker. In 93 patients (32 per cent) there were significant nonfatal complications which required secondary procedures for correction. This summary is intended to make only the point that, despite an approximately 30 per cent incidence of technical difficulties, only 3 per cent of a large group of patients with symptoms due to heart block died of this disease in an average observation period of approximately 1 to 3 years. Operative mortality would add slightly to this figure and there is a significant mortality from unrelated causes in this group of generally elderly patients. Nevertheless, these patients usually had syncope or other circulatory failure which was refractory to pharmacologic agents. A mortality in the range of only 3 per cent from the disease or from complications of its treatment in such a period undoubtedly represents an improvement over previous reports of the natural history of this disease.[7]

In summary, the safety and efficacy of implanting artificial pacemakers is again documented. This is a strong argument for the early use of implanted pacemakers in patients with syncope caused by heart block. At the same time a variety of problems have occurred. Some of these have probably been eliminated by improvements in instrumental design and other improvements may be expected. Other factors require consideration in the choice of treatment for heart block. A significant number of these patients die from diseases unrelated to their heart block. A significant number of them lead sedentary lives and a brief trial of drugs is permissible even if not found to be effective. In such instances the physician will have to accept the responsibility for the very slight possibility that a second or third syncopal attack during a trial of drugs could be fatal. Failure of vagolytic or adrenergic agents to reduce block or accelerate an idioventricular focus initially is probably an indication of later failure of long-term nonoperative management. The patient's acceptance of surgery is likely to be enhanced if he knows that nonoperative measures have been unsuccessful. On the other hand, a relatively young and active individual is more likely to require the most reliable and immediate protection available against recurrent syncope. This would consist of pacemaker implantation at the present time. Each of these several factors must be weighed in the management of patients with heart block.

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Hypertension and multiple renal arteries

A great deal of interest has been centered recently on the significance of multiple renal arteries in hypertension.

Each kidney is usually supplied by one artery which arises from the aorta and is derived from the network of vessels supplying the mesonephros of the embryo More than one artery may be present, and the maximum number expected in either kidney from a study of their development is five. One such case has been recorded at autopsy (Hauter 1901 quoted by Sykes[17]) and the largest number recorded angiographically is four.[18]

Estimates of the incidence of multiple arteries at autopsy in nonhypertensive subjects have been based on reviews of the literature, and vary from 26 per cent kidneys[2] to 30 per cent kidneys.[19] Angiographic studies in which hypertension was not an indication for the investigation have estimated the incidence between 21 per cent kidneys and 26 per cent kidneys. The incidence is lower in the angiographic series because, although most people have renal arteries arising from the suprarenal, spermatic, and superior mesenteric arteries, which can be shown at autopsy these are too small to be visible on an angiogram. These figures provide a reliable point of reference for comparing other series. Unfortunately direct comparison is impossible if the results are expressed in terms of patients and not kidneys, [a,b,c] because renal arteries are unilateral in some patients but bilateral in others, so that the incidence in terms of patients will always be greater than i terms of kidneys. Attempts to compare the two groups directly have been confusing.[a] Marshall[a] found a significantly higher incidence of multiple renal arteries among the hypertensive patients i his autopsy series (86 per cent) than among the nonhypertensive patients (49 per cent). These incidences are far higher than in any other series, nd this is partly because he included pre-hilar branching of a single artery as did Derrick and Tyson, who reported multiple arteries in 52 per cent of hypertensive patients. There is no justification for doing this, nd it invalidates direct comparison with other series.

Renal angiography in hypertensive patients ha also produced conflicting results. The incidence of multiple arteries has varied from 14 9 per cent, using translumbar aortography to 50 per cent, using nonselective catheterization. Davis and associates, reporting their experience with both methods, found multiple arteries in 18.5 per cent of 85 hypertensive patients examined by aortography and in 34 7 per cent of 167 hypertensive patients examined by nonselective catheterization They infer that lumbar aortography is an inferior method of investigation and estimate that the true incidence of multiple arteries among hypertensive patients is 35 per cent.

In a recent report, the angiograms of 550 hypertensive patients (1,089 kidneys) and 115 nonhypertensive patients (225 kidneys) were reviewed in detail. There was no significant age sex, or side incidence of multiple arteries among the hypertensive patients Sixty two per cent of the arteries arose below the main artery and 66 per cent arose within 3 cm. on either side of the main artery the greatest distance between an accessory artery and the main artery was 12 cm. Multiple arteries were present in 32.55 per cent of hypertensive patient (19.55 per cent kidney) and in 32.18 per cent of nonhypertensive patients (20 25 per cent kidneys) There was no significant difference between the two groups, and both groups agree closely with the estimates in other major series,[a] indicating that the frequency of multiple renal arteries is the same in hypertensive and nonhypertensive patients.

Three methods were used to investigate these cases. translumbar aortography selective catheterization and nonselective catheterization There was no significant difference in the incidence of multiple arteries whatever the method of investigation. Indeed, it is difficult to see why lumbar aortography should be inferior to nonselective catheterization, provided that the aorta is adequately filled. The main criticism of selective catheterization is that multiple arteries may be overlooked However their presence can be inferred from the absence of some arterial branches or the presence of an incomplete nephrogram.[a] The use of tapered catheter with side holes gives some filling of the aortic lumen enabling the origins of multiple arteries to be identified, and it is then often possible

to catheterize each one If this proves to be im possible a free injection should be made into the aortic lumen before withdrawal of the catheter It is then unlikely that multiple rteries will be overlooked Selective theterization gives better and more detailed isualization of the renal vessel and is therefore, to be preferred

Despite the conflict of some of the evidenc the view generally supported is that multiple arteries are as common in hypertensive a in nonhypertensive patients, and that the method of investig tion does not affect the result

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Pumping action of pulmonary veins

In 1934 Burch and Romney[1] described sphincter like muscular sleeves around pulmonary eins in man and suggested that these eins may ha e a throttle valve action. I 1958 Eliakim Rosenberg and Braun[2] demon trated in dogs that the intravenou injection of hypertonic saline ca sed a rise in pulmonary venous pressure whereas the left atrial pressure either remained unchanged or was decreased. The development of this pressure gradient wa thought to be due to spasm of the pulmonary vein-left atrial junction. Parker Steiger and Friedenberg[3] recently demonstrated pulmonary venomotion in vivo in dogs by select e pulmonary phlebography before and after infusion of serotonin. These authors al-o reviewed evidence available in the literature which confirms that the pulmonary veins may con strict under certain circum tances, and therefore play a important role i the regulation of pul monary hemodynamics

As mentioned above pulmonary enous hyper ten ion was accompanied by an increment in the pulmonary vein left trial pressure gradient I e left atrial pressure either decreased or did not change at ll. The systemic arterial pressure and systemic blood flow frequently decreased in these experiments. These findings indicate therefore that pulmonary venoconstriction by having a closure-like effect may cause diminished inflow of blood into the left heart and thus decrease left ventricular output

The results of these experiments suggested to us that pulmonary venoconstriction may be variable under certain circumstances, and may also cause an increased inflow into the left heart with a subsequent rise in the left atrial pressure. In order to achieve a lesser degree of pulmonary venoconstriction and a rise in both the pulmonary venous and the left atrial pressures, we planned experiments with intravenous injections of hypertonic saline which were smaller in volume than those that we had used in our previous studies.[4] These experiments were performed on anesthetized open-chest dogs under artificial respiration. Pulmonary venous, left atrial, and systemic blood pressures were measured simultaneously with pressure pulses and mean pressures being recorded. Pulmonary as well as aortic mean blood flow were obtained with the aid of a rotameter (Clifford Wilson). Intravenous injection of 20 per cent saline in quantities of 0.5 to 1.0 c.c. per kilogram was given. In the greater number of our experiments pulmonary venous pressure rose by 3 to 6 mm., which was lower than we had found previously. Since this rise in pressure occurred without a change in pulmonary blood flow, it indicated active pulmonary venoconstriction. This was followed by a similar rise in the left atrial pressure and an increase in systemic pressure. Together with these changes, an increased systemic blood flow was noted.

From the findings described above, it is evident that the pulmonary veins, in certain circumstances, have a pumping action and thereby cause an increase in the pulmonary venous return. Thus augmented inflow of blood into the left atrium is followed by an increased left atrial pressure and increased left ventricular output. It may be concluded, therefore, that the pulmonary veins are an integral part of the circulation and may play an important role in the regulation of cardiovascular performance. Thus, the function of the pulmonary venous system seems to be not different from that of the peripheral veins.

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A critique of the equivalent cardiac generator

Electrocardiography is concerned with a determination of the clinical meaning of the surface potentials on the human torso due to the electrical activity of the heart. The underlying phenomena is that the heart muscle behaves as a source of electromotive force (emf) which, in turn, causes a flow of current in the surrounding passive media and in this way establishes the observed surface potential field. Although the ultimate goal is information on the physiologic condition of the heart, this is clearly related to its electrical behavior. Thus an intermediate goal in electrocardiography is the determination of as complete a description as possible of the electromotive forces in the heart.

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A description of the actual electrical sources in the heart would, at the very least, be extremely complicated. Thus, what is actually sought is some simple, although approximate, representation which is equivalent to the actual sources. Equivalence is usually taken to mean that within a homogeneous torso the equivalent cardiac generator sets up the same surface potential distribution as is set up by the real heart in the real body.

Since its earliest beginnings the equivalent source has been chosen to be a dipole that is fixed in position within the heart although variable as to magnitude and position. A great amount of evidence supports the adequacy of this model. However, in recent years the limitations of a simple dipole have been pointed out, and efforts to develop clinically useful but more elaborate representations have been considered.

Studies on the nondipolar components of the true heart sources have led to equivalent generators of more complex nature. Examples of these include multiple dipoles, moving dipoles, electromotive surfaces, and multipoles. Implied in this point of view is the notion that if the true sources were known, then the equivalent source would arise from them as a simplifying approximation. The problem essentially is being considered, so to say, from "inside-out," from the generator to the potential field.

Now this point of view can lead to serious difficulties in electrocardiography. This is because the information that is available is the surface potential distribution itself; the problem is actually "outside-in." Accordingly, the electrical model of the heart must be limited to those whose parameters can be uniquely determined from measurements on the torso surface. Now potential theory furnishes an explicit statement on this question, namely, that surface potential measurements serve to determine *only* the spherical harmonic multipole expansion of the sources.* In other words, so far as electrocardiography is concerned, the moving dipole, multiple dipole, electromotive surface models are meaningless, since surface potentials are not capable of unambiguously specifying them.

The introduction of multipole analysis into electrocardiography was done by Wilson about 20 years ago, and considerable progress has been made since, notably by Geselowitz and Brody. Although the fact that the multipole model is the *only* valid equivalent cardiac source in electrocardiography is relatively well recognized, efforts to develop other models continue. This is probably partly a result of the sophisticated mathematical argument required to recognize why the above-mentioned result is true and to show the specific errors in other systems.

These conclusions imply, unfortunately, that the available information from an electrocardiogram is limited. The multipole expansion has as its leading term the conventional dipole, and the next correction term is a quadrupole. It is possible that with great care a clinical lead system may be found that could measure the quadrupole components. This would increase the number of parameters (at any instant) from three to eight and might result in much improvement in diagnosis. But even if the infinite number of multipole coefficients could be measured, it would not yield the actual distribution of heart sources.

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*The remarks in this note are restricted to an electrocardiographic system based on measurements made on the body surface. They would also apply, in general, to the electrogram. If electrodes are inserted into the heart, however, these restrictions no longer apply and the actual electrical sources could be explored. But such a diagnostic tool would be of a different nature than that embodied in classic electrocardiography.

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Book reviews

THE PHARMACOLOGICAL BASIS OF THERAPEUTICS. Edited by Louis S. Goodman M.A., M.D., Professor and Chairman, Department of Pharmacology University of Utah and Alfred Gilman, Ph.D., William S. Ladon Professor and Chairman, Department of Pharmacology Albert Einstein College Third edition, New York, 1965 The Macmillan Company 1785 pages. Price $22.50

The third edition of this excellent book by two outstanding pharmacologists is welcomed. This edition continues the same principles established initially of emphasizing the pharmacologic aspects of therapy The chapters are documented by good bibliographies, and of course, the new drugs are included in this edition Every physician should have this book in his office for frequent use as reference.

YEAR BOOK OF CARDIOVASCULAR AND RENAL DISEASES, 1964-1965 Chicago, 1965 Year Book Medical Publishers, Inc 477 pages. Price $10.

This book is an excellent summary of the important papers published last year on cardiovascular and renal diseases As would be expected in so small a book, only summaries of a relatively few papers could be included. Nevertheless, this is a useful book for those who find it impossible to follow closely the literature and still conduct their daily work. This is a good book and should prove to be useful to all in the cardiovascular and renal fields as well as to internists, general practitioners and surgeons.

VASCULAR SURGERY By Herbert R. Hawthorne M.D Emeritus Professor and Chairman Department of Surgery Graduate School of Medicine, University of Pennsylvania. Springfield, Ill. 1965 Charles C Thomas, Publisher 249 pages. Price $18.75.

This is a compendium of papers presented at a symposium on vascular surgery There is nothing new in this book. The many chapters consist of short papers which deal with such subjects as genesis of atherosclerosis, current concepts of atherosclerosis, anticoagulant therapy arteriography grafts, mechanized suturing of blood vessels, patent ductus arteriosus, coarctation of the aorta, embolism, and renal vascular hypertension. Very little critical evaluation of these important problems is presented, and in most instances the presentations are extremely brief

DIFFERENTIAL DIAGNOSIS OF CARDIOVASCULAR DISEASE. By Aldo A. Luisada, M.D., Professor of Medicine, Chicago Medical School and Sheldon J Sodia, M.D., Assistant Professor of Medicine Chicago Medical School. New York, 1965 Grune & Stratton, Inc., 226 pages. Price $9 75

This short book is the outgrowth of a series of lectures prepared by the authors. It is intended primarily for upperclassmen in medical schools, and for house officers.

The organization is entirely in the format of a list of individual differential diagnoses, e g "aortic stenosis causing right heart failure vs. Bernheim syndrome or rheumatic tricuspid stenosis or insufficiency vs. that caused by carcinoid heart disease. There is therefore, inevitably a large amount of repetition Some of the features of mitral stenosis for instance, are covered fifteen or twenty times

There are no illustrations and no bibliography

This book does not have the authoritative presentation and logical readable style necessary in a work which is to serve the student as an introduction to clinical cardiology Its greatest potential usefulness is for those who have a specific diagnostic problem in mind, e.g., "hyperkalemia vs. true posterior infarct and who are able to locate and use an appropriate section in this book.

PULMONARY EMBOLISM MECHANISM AND MANAGEMENT By Robert Marshall, M D First Assistant, Nuffield Department of Surgery Radcliffe Infirmary Oxford, England Springfield, Ill 1965 Charles C Thomas, Publisher 163 pages. Price $7

The author of this short book on pulmonary embolism discusses the subject clearly and briefly and includes almost 500 references in the bibliography There are 11 chapters in the 127 pages. He discusses historical aspects of embolism origin of emboli, the pathologic physiology of pulmonary embolism pulmonary infarction diagnosis, prevention, and treatment.

He concludes on page 127 with the statement that Perhaps the most depressing feature of research on pulmonary embolism, over the last 120 years, is the failure to provide any effective method for reducing the incidence of embolism that the available methods of anticoagulant treatment are inadequate This discouraging statement is unfortunately true

This is a good book

RÖNTGENOLOGISCHE HERZVOLUMENBESTIMMUNG IN KLINIK UND PRAXIS. By Prof Dr Helmut Kleprig and Dr Peter Frisch Stuttgart 1965 Georg Thieme Verlag 54 pages.

This is a small but very good book which describes in German the radiologic method for determining the volume of the heart. The authors describe the concept, technique interpretation, and application of measurements of the volume of the heart of patients The illustrations are many and excellent. This book should be of value to radiologists, cardiologists internists, and general practitioners.

CARDIOVASCULAR PATHOLOGY. VOLS. I AND II. By Reginald E. B Hudson, M D P thologist to the Institute of Cardiology University of London Baltimore 1965 Williams & Wilkins Company 2123 pages. Price $60 per set

This two-volume set of books on cardiovascular pathology is excellent The author not only discusses the histopathology and gross pathology but includes pathophysiology as well. The latter is the weak aspect of the book, however For example on page 279 Dr Hudson attempts to present the mechanism of the formation of edema in congestive heart failure. Not only does he fail to review the literature adequately but he also fails to say anything worth while The bibliography throughout the book is incomplete and quite superficial, the references usually include only recent papers and rarely papers which appeared before 1950 His discussion of pulmonary edema (page 282) is limited to three sentences which are not even worth reading These deficiencies in pathologic physiology detract from an otherwise good set of books. The illustrations are numerous, the diagrams clear and also good The two volumes include a discussion of practically all types of heart disease. This is a good set of books which should especially interest pathologists and cardiologists.

PROGRESS IN RESEARCH IN EMPHYSEMA AND CHRONIC BRONCHITIS. VOL. 2 THE PATHOGENESIS OF THE CHRONIC OBSTRUCTIVE BRONCHOPULMONARY DISEASE. Edited by Roger S. Mitchell and H Herzog Denver Colo. New York 1965 S. Karger 431 pages. Price $21 90

This is the proceedings of the Seventh Annual Conference on Research in Emphysema held in Aspen Colorado during June of 1964 Among the many problems discussed were clinical and environmental studies, alveolar surfactant, pulmonary circulation lung morphology and structure-function relationship. This is a good book Not only have the contributors presented their views clearly but they have supported them with good and concise illustrations in short presentations. The bibliographies are good, and discussions are included which adds to the value of the book. This book should be of value not only to the physicians and investigators interested in the lungs but also to those in the field of cardiology

Books received

THE PILLS TO KEEP WOMEN YOUNG. By Ann Walsh, New York, 1965 Bantam Books Inc., 178 pages. Price 75¢

MEDICAL SOUND RECORDINGS. By John Graves and Valerie Graves Baltimore 1964 Williams & Wilkins Co., 160 pages. Price $12

MODERN TREATMENT Vol. 2 No. 5 September 1965 Treatment of Skin Diseases by D Joseph Demis Treatment of Chronic Disturbances of Bowel Function by J Alfred Rider and Hugo C. Moeller New York 1965 Hoeber Medical Division Harper and Row Publishers. Bimonthly by subscription only Price $16 per year

RESPIRATORY THERAPY By Peter Safar Philadelphia 1965 F A. Davis Co., 419 pages. Price $7.50

ULTRASONIC ENERGY By Elizabeth Kelly Urbana 1965 University of Illinois Press 388 pages. Price $12.50.

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Editorial

Platelet stickiness

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The aggregation of platelets is the first change which occurs in blood during the formation of a thrombus. Direct observation of experimentally traumatized vessels, in a variety of animals, showed that the white body which formed at the site of the intimal injury was composed of closely packed platelets without visible linking processes.[1] Thrombus, being the material formed in a blood vessel from the circulating blood elements as distinct from clot which is formed when blood solidifies outside the body, may be produced in vitro by means of the Chandler technique[2]: blood anticoagulated with citrate is placed in a closed plastic loop, calcium to neutralize the anticoagulant is added, the plastic tubing is rotated, and the blood eventually solidifies. This solidified material has the histologic appearance of naturally occurring thrombus. The formation of these artificial thrombi has been studied with the electron microscope and it was confirmed that in the initial stages the closely packed platelets retained their normal shape and that the formation of fibrin, as in a clot, was absent in the platelet masses. However, it has been reported by other workers that the formation of fibrin occurred very early in the hemostatic mechanism (15 seconds) and at a time when few platelet aggregates could be defined.[4] This phenomenon of platelet aggregation is reversible, since dispersal of aggregated platelets has been observed, and dispersed platelets when studied by phase-contrast microscopy have shown no abnormality.[5] Mustard and his associates,[6] through the use of radioisotope double labeling techniques, have, in elegant experiments, demonstrated that platelets involved in an artificially induced thrombotic state in the intact animal may be returned to the circulation.

If dispersal of the aggregated platelets does not occur, then the next stage in thrombus formation is the amorphous fusion of the platelet clump—viscous metamorphosis.[7] It is probable that this change in the morphologic appearance of the platelet mass is associated with the liberation of platelet factors, particularly phospholipids. These compounds, together with the stasis induced by the impermeability of the altered platelets, initiate the processes of blood coagulation which culminate in the formation of fibrin. White and red cells become enmeshed in the framework of fibrin threads and thrombus is formed. The initial stage in thrombus

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formation is completely independent of plasma coagulation but depends on platelet function and plasma factors which are not clotting factors.[4] This, and the recognition that the aggregation of platelets is a potentially reversible phenomenon has opened new concepts for the possible prevention of thrombosis.

The most fundamental observation in the laboratory study of platelet aggregation was the demonstration that minute amounts of adenosine diphosphate when added to platelet-rich plasma would cause the platelets to aggregate. Hellem[8] in 1960 showed that an extract of red cells which was acidic, dialyzable, and heat stable caused aggregation of platelets; the following year by application of chromatographic techniques for nucleotide separation it was shown that this substance was adenosine diphosphate (ADP).[9] It had previously been shown that platelets contained large amounts of adenosine triphosphate (ATP)[11] and that if they underwent viscous metamorphosis, or were suspended in plasma which was clotting, most of the ATP was rapidly broken down.[12,13] It is probable that the breakdown of platelet ATP leads to the formation of ADP,[4] and thus the platelets themselves are a potentially rich source of ADP. Red blood cells as a source of adenosine diphosphate have tended to be overlooked, but the contribution of ADP from this source may be important in view of their proportionately greater mass and number.[4]

Born[5] described a very sensitive technique by which aggregation may be studied. Platelet-rich plasma is placed in a container in which a stirring device is rotating (aggregation occurs in a system in which the platelets are moving, since a collision force is necessary); a beam of light is shone through the specimen, and the optical density of the platelet-rich plasma is recorded at frequent intervals; if aggregation occurs, then the optical density decreases, whereas if the clumped platelets disperse, there is a rise in optical density. Through the use of this technique or a modification, it has been confirmed that adenosine diphosphate will cause the aggregation of platelets.[15] Aggregation is also obtained with 5-hydroxytryptamine (5-HT), norepinephrine, and epinephrine hydrochloride[13] (these substances are carried by platelets), by thrombin,[16] by triethyltin,[17] and by fatty acids[18]; it has also been shown that the addition of collagen fibers to platelets induces aggregation.[19] A report that ATP caused platelet aggregation[15] was not confirmed[20] and it is possible that some preparations of adenosine triphosphate may have been contaminated with adenosine diphosphate.[21] Whether these compounds which cause aggregation act by a final common pathway, namely, the liberation of adenosine diphosphate, is not clear. It has been shown that if the accumulation of adenosine diphosphate is prevented by the pyruvate kinase and 2 phosphoenol pyruvate system, then the aggregating ability of thrombin and fatty acids is inhibited.[18] O'Brien[22] studied the kinetics of aggregation produced by various compounds, ADP, thrombin, 5-hydroxytryptamine, epinephrine, norepinephrine, and triethyltin, and concluded that the results suggested that aggregation produced by the compounds studied was accompanied by liberation of diphosphate from the platelets. In a recent excellent review, Sharp[23] has summarized the position. Although the unitarian theory now appears the most attractive, there is some evidence that the behaviour of aggregates and morphology is not the same in all systems.

That the ability of adenosine diphosphate and other substances to cause platelet aggregation is more than an interesting laboratory phenomenon is shown by the demonstration that, after the traumatization of an artery to a degree insufficient to cause the formation of white bodies at the site of the injury, these bodies would appear if either ADP, ATP, or 5-HT was applied to the area of injury.[22] Although the factors influencing the aggregation of platelets are of fundamental interest and importance, it is the factors influencing the dispersal of aggregated platelets which may be of immediate interest to clinicians. Adenosine and related substances, notably adenosine monophosphate, 2-chloroadenosine, 2 bromoadenosine, and 2 fluoroadenosine, have the ability to inhibit ADP-induced aggregation[24]; antiserotonins inhibit the aggregation induced by 5 hydroxy-

tryptamine and phentolamine, that by epinephrine and norepinephrine.[22] In the experimental animal adenosine and 2-chloroadenosine have been found both to prevent the formation of and to disperse white bodies in injured arteries.[23] However adenosine and certain of its analogues cause serious side effects, such as hypotension and respiratory arrest, in certain laboratory animals.[23,24] This, coupled with the recent demonstration that the relative ability of adenosine and its derivatives as inhibitors of platelet aggregation was related to their potency as vasodilators[26] must make it doubtful that such compounds will be of immediate application in the prevention of intravascular thrombosis.

The importance clinically of the role of platelets in the initiation of intravascular thrombosis antedates much of the above-mentioned work, which has been related mainly to the study of platelet aggregation in vitro or in the experimental animal. The first attempt to apply some test of platelet function to a clinical situation in which thrombosis was especially liable to occur was by Helen Payling Wright. In 1941[27] she described a technique whereby the adhesion of platelets to a glass surface was measured—platelet adhesiveness (in recent studies usually referred to as platelet stickiness). Blood anticoagulated with heparin was placed in a glass bulb which was slowly rotated; a platelet count was made prior to and after rotation and the final count was expressed as a percentage of the initial platelet count. She found that in the postoperative and postpartum periods the stickiness was increased, that is to say, that an increased percentage of platelets adhered to the glass surface.[28] These original observations have recently been linked with the experimental systems involving ADP aggregation. Platelets from patients in the postoperative phase showed an increased response to aggregation by adenosine diphosphate, adenosine triphosphate, noradrenaline, and 5-hydroxytryptamine.[29] This was the first work in which aggregation dependent on ADP and related compounds was studied in patients at high risk of thrombotic disease, and it is of interest that the two techniques, the one measuring the adhesion of platelet to platelet, the other platelet to glass, gave similar results in the same clinical situation. A modification of the technique devised by Wright has been applied by McDonald to the study of patients with ischemic heart disease. These subjects showed a definite increase in platelet stickiness over normal control subjects[30] and after a period of 5 to 6 weeks on a low fat (rice and fruit) diet returned to normal the increased stickiness levels.[31] Further interesting observations by McDonald and his co-workers[32] linked increased platelet stickiness with decreased activity of lipoprotein lipase as a familial defect in subjects with ischemic heart disease. Since lipoprotein lipase is a major pathway for clearing alimentary lipemia, this finding emphasized the importance of blood fats in relation to platelet stickiness. Owren and associates[33] found increased platelet adhesiveness in subjects with diabetes and atherosclerosis and studied the effect of the administration of linolenic acid. The platelet adhesive index was measured by passing platelet-rich plasma, to which ADP had been added, through a column of glass beads under carefully standardized conditions and calculating the percentage of platelets recovered. Six hours after a single dose of 30 ml. of linolenic acid a decrease in platelet adhesiveness was noted and if 20 ml. was given daily for 3 days or 5 ml. for 7 days, the levels of platelet adhesiveness returned to normal. Reports on the value of linolenic acid in the prevention of thrombosis will be awaited with great interest. The relationship between the dietary intake of fat and blood coagulation tests, including platelet survival as measured by radioactive diisopropyl fluorophosphonate (DFP), has been studied by Mustard and Murphy.[22] Platelet survival was shortened and the activity of in vitro tests of blood coagulation increased when the diet was high in dairy fats and eggs; the decreased platelet survival would suggest active utilization of platelets in a thrombotic process.

There are many reports of correlation between the national consumption of fat and the incidence of ischemic heart disease.

*See addendum.

However, it has been proposed by Yudkin that this association may be secondary to the parallelism between the national consumption levels of fat and sugar, and, furthermore, that the level of sugar intake may be related to the development of ischemic heart disease.[34] An association between carbohydrate metabolism and platelet stickiness has been demonstrated. Through use of the technique of McDonald,[36] it was found that platelet stickiness was increased in subjects with diabetes mellitus, and also that, both in normal and diabetic subjects, a rapid rise in blood sugar produced by administration of glucose was associated with an increase in platelet stickiness.[35]

In the above-mentioned series of experiments, as with many of those involving modifications of intake of fat, it would seem that platelet adhesiveness reflects changes in the medium in which the platelets are circulating. The rise in platelet adhesiveness found by Wright in the postoperative and postpartum period was maximal at about the same time as the maximal rise in platelet count, and it was suggested that young platelets may be more adhesive. Evidence to support this view can be found in the work of Murphy and Mustard.[36] Thus, it would seem that platelet adhesiveness may be an indicator of a hypercoagulable state which is influenced not only by changes in the plasma but also by changes in the platelets themselves.

Interpretation of studies of platelet function in patients with hemorrhagic diatheses is rendered difficult by the use of different terminologies to describe these various syndromes. Through the use of a technique which measured the percentage of platelets recovered when uncoagulated blood was passed through a glass filter, it was found that patients with classic hemophilia, Christmas disease, Hageman factor deficiency, and Factor VII deficiency showed no defect in platelet adhesiveness.[37] In regard to the present context, perhaps the most relevant clinical disorder of hemostasis is thrombasthenia, a congenital disease characterized by a normal platelet count, prolonged bleeding time, and impairment of clot retraction. Platelets from these patients failed to adhere to a glass surface or to show the normal aggregation when exposed to adenosine diphosphate, 5-hydroxytryptamine, norepinephrine, or thrombin.[38] The platelet ATP content has been reported to be normal,[38] whereas other workers have found it to be sharply reduced, this reduction being associated with lowering of certain glycolytic enzymes, namely, glyceraldehyde phosphate dehydrogenase and pyruvate kinase.[39] The further definition of the biochemical relationships in thrombasthenic platelets could make some contribution to the understanding of the factors which determine platelet aggregation.

The influence of anticoagulants on platelet adhesiveness has been reported by many workers. A low dose of heparin (1,500 units twice weekly) was found to cause a lowering of increased levels of platelet stickiness.[40] Murphy and Mustard, however, found no change in platelet adhesiveness or platelet survival using this dose,[41] but had previously reported that these parameters were favorably influenced by larger doses of heparin (8,000 units every 8 hours).[42] In the rabbit it was found that after the administration of heparin sufficient to cause marked prolongation of the clotting time the formation of white bodies at the site of intimal injury was not affected.[1] The addition of heparin to human platelet-rich plasma in a Chandler tube caused significant prolongation of the time required for platelet aggregation; platelet-rich plasma from patients who were receiving adequate therapeutic doses of warfarin and phenindione also had significantly prolonged aggregation times.[43] Murphy and Mustard found that subjects on intensive dicoumarol therapy had a decrease in platelet adhesiveness, whereas with low doses, although slight prolongation of prothrombin time was produced, platelet adhesiveness was increased.[44]

The adhesive properties of platelets have been studied in certain diseases in which it is unlikely that the basic defect lies in thrombogenesis. The addition in vitro of an encephalitogenic factor derived from human brain to plasma from patients with multiple sclerosis during the active phase of the disease caused increased stickiness of platelets, whereas if the disease was quiescent, no change occurred. It was

also noted that serum from subjects with hepatic cirrhosis gave similar findings.[45]

In summary it may be said that the fundamental role of platelets in the initiation of thrombosis has been demonstrated by the use of morphologic techniques. The advances gained by the application of biochemical techniques to the study of the first changes which occur during thrombogenesis have been spectacular and it is to the application of these techniques that one must look for advances in knowledge in regard to the formation of thrombi and its prevention.

Addendum

In view of the potential importance of these results, attention is drawn to two subsequent papers. In later work Owren and associates[46] reported that the previous results indicating a uniform effect of linolenic acid in reducing platelet adhesiveness had not been confirmed. Similar negative findings have been recorded by Borchgrevink and associates.[47]

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Clinical communications

Pyridinolcarbamate, a bradykinin antagonist in veins

A preliminary report on pharmacologic and clinical observations

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Recent experimental data accumulated on bradykinin and its active homologues[1-4] suggest that it is an important factor in the pathogenesis of several seemingly unrelated clinical disease processes. In such disease states in which bradykinin assumes an important pathogenetic role, a bradykinin antagonist would appear to be a highly desirable agent, both for prophylaxis and therapy. To date no such antagonist has been available.

Recently Ishikawa and his associates synthesized several compounds which demonstrated anti-inflammatory properties. These compounds were extensively studied in our laboratory and an unequivocal antagonistic effect was demonstrated on the venoconstrictive properties of bradykinin and lysylbradykinin. Of these compounds, pyridinolcarbamate appeared to be the most effective and was associated with only minimal toxicity.

The present communication deals with a brief summary of the pertinent pharmacologic properties of pyridinolcarbamate and the results of the clinical use of it on 90 hospitalized subjects in the authors' university hospital.

Laboratory studies

Chemical property. Pyridinolcarbamate is a weak basic synthetic compound which has been chemically characterized as 2,6-bis(hydroxymethyl)pyridine bis(N-methylcarbamate). It is an odorless nonhygroscopic white crystal with a melting point of 136 to 138°C. The crystal and its neutral solution are stable and can be stored at room temperature.

Pharmacologic property. The LD_{50} of

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pyridinolcarbamate per os is 1 000 mg per kilogram in dogs, 5 200 mg per kilogram in rabbits 3 400 mg per kilogram in rats, and 4 500 mg per kilogram in mice Pyridinolcarbamate administered to dogs at doses of 300 mg per kilogram for 10 weeks did not result in any adverse tissue reaction A similar result was obtained in rabbits after doses of 800 mg per kilogram for 10 weeks.

Bradykinin-antagonistic effect

IN VITRO The vasoconstrictive property of bradykinin was first mentioned by Burch and DePasquale[7] in the arteriovenous anastomoses of human finger tips and thereafter Guth and associates[8] observed the venoconstrictive response of rabbit ear veins to bradykinin Rowley[9] found that venoconstriction induced by bradykinin in rats resulted in the leakage from leaking vessels.[10, 11] The author found a highly potent venoconstrictive effect of bradykinin and lysylbradykinin in several species of animals. The perfused vein preparations of the ear saphenous, or coronary vessels of rabbits, and the coronary veins of dogs perfused with Ringer Locke solution (37°C) at a pressure of 150 mm of water were found to be highly sensitive to bradykinin and lysylbradykinin In the saphenous or ear vein preparations 0 002 µg per milliliter of synthetic lysylbradykinin or 0 005 µg per milliliter of synthetic bradykinin and in coronary vein preparations 0 05 µg per milliliter of synthetic bradykinin or lysylbradykinin induced a marked constriction of the isolated vein and effectively reduced the outflow of perfusate from the vein preparation The effect is persistent (no tachyphylaxis) related to the doses applied and reproducible on a quantitative basis. Through the use of such a preparation the specific antibradykinin and antilysylbradykinin effect of pyridinolcarbamate was clearly demonstrated Perfusion with pyridinolcarbamate dissolved in Ringer Locke solution in a concentration of 50~100 µg per milliliter resulted in a mild but specific inhibitory effect on the venoconstriction induced by bradykinin and lysylbradykinin In a concentration of 400 µg per milliliter it potently inhibited the venoconstrictive effects of bradykinin and lysylbradykinin The replacement of pyridinolcarbamate perfusate with Ringer Locke solution resulted in a rapid restoration of the sensitivity of the vein to bradykinin This antagonistic effect of pyridinolcarbamate was competitive[14] and reversible and appears to be limited to the vein In our studies, pyridinolcarbamate either antagonized very slightly or did not antagonize the effects of bradykinin on the motility and tone of smooth muscle of other organs [15-18]

IN VIVO The dermal injection of bradykinin lysylbradykinin histamine and serotonin has been extensively studied in rabbits, rats, guinea pigs, dogs, and cats by the method of Miles and Miles.[19] It was found that the mixing[20] of pyridinolcarbamate with bradykinin lysylbradykinin or kallikrein solution in a concentration of 50 to 250 µg per milliliter inhibited the leakage of dye

Mixing pyridinolcarbamate with histamine or serotonin did not prevent the leakage induced by histamine or serotonin

The oral administration of pyridinolcarbamate in a dose over 30 mg per kilogram to guinea pigs exhibited a specific inhibitory effect on the leakage of dye of high molecular weight [9, 10, 21] such as Evan s blue at the site of injection of bradykinin lysylbradykinin or kallikrein On the other hand leakage of dye after the dermal injection of histamine or of serotonin was not prevented by pyridinolcarbamate. Also, the accumulation of leukocytes at the site of dermal injection of bradykinin (10 µg in 0 1 ml)[22] in rabbits was effectively prevented by the oral administration of 100 mg per kilogram of pyridinolcarbamate

Pyridinolcarbamate in an intravenous dose of 30 mg per kilogram was also shown to exert a specific preventive effect against the pseudoaffective response[23] induced by bradykinin in rabbits. Pseudoaffective response is characterized by hyperpnea struggling and crying induced by bradykinin However this drug afforded no protection against the pseudoaffective response induced by acetylcholine. It is not yet known whether this is due to a direct bradykinin antagonistic effect or an indirect preventive effect against venous leakage induced by bradykinin

Anti inflammatory activity of pyridinolcarbamate is not easily demonstrated by the usual laboratory models of inflamma

tion although pyridinolcarbamate exhibited a moderate anti inflammatory activity in carrageenin foot edema of rats.[22] The local application of pyridinolcarbamate in concentrations as low as 0 004 per cent effectively inhibited the inflammatory response produced in the skin of guinea pigs by passive cutaneous anaphylaxis with egg albumin. The degree of inhibition of the inflammatory response by pyridinolcarbamate was dose dependent. From these observations it appears that pyridinolcarbamate effectively blocks inflammatory (vascular) responses involving body immune mechanisms. It is well known that such inflammatory responses have been implicated in the pathogenesis of certain clinical conditions.

In the edematous arterial reaction[24-26] induced in animals by the administration of epinephrine or cholesterol or by trauma (crushing of thigh muscles) pyridinolcarbamate in an oral dose of 5 mg per kilogram was shown to exhibit a unique preventive effect whereas corticosteroids antihistaminics, and an antiserotonin agent (cyproheptadine) remained without effect

Pyridinolcarbamate in Lindner's test[27,28] Intravenous administration of vasopressin in rats in a dose of 0.5 U per kilogram induces electrocardiographic signs of ischemia, an asphyctic T wave (a strongly positive T wave accompanied by elevation of S-T segment) and subsequent S-T depression The pretreatment of rats with intravenous pyridinolcarbamate in a dose of 0 1 mg per kilogram significantly reduced the height of the asphyctic T wave ($p < 0.05$) Larger intravenous doses of 1 mg per kilogram not only reduced the height of the asphyctic T wave, but also prevented the S-T depression ($p < 0.01$) However hypertensive and successive hypotensive responses induced by vasopressin in the rat remained unchanged by pretreatment with pyridinolcarbamate

Antiatherosclerotic effect An oral dose of pyridinolcarbamate (5 mg per kilogram per day) has been repeatedly shown in our laboratory to inhibit atheromatous changes in rabbits maintained on a high-cholesterol diet The rabbits were maintained on a high-cholesterol diet for 15 weeks, and the average level of serum cholesterol during the latter part of the study exceeded 2,000 mg per deciliter The content of cholesterol in the whole aorta was determined and found to be strikingly reduced in rabbits treated with pyridinolcarbamate ($p < 0.01$) This study has been repeated on four separate occasions in the authors laboratory during the past 2 years with similar results. The total number of experimental rabbits now exceeds 250

Antithrombotic effect The administration of epinephrine or animal fat or the traumatization of animals[29] induces a shortening of the one-stage prothrombin time calcium clotting time and Lee White clotting time, and a decrease in the adhesive platelet count These changes were effectively prevented by pretreatment of the animals with pyridinolcarbamate in a dose of 1 to 10 mg per kilogram orally Pyridinolcarbamate also inhibited the formation of thrombus in a new experimental model[30] without exerting demonstrable effect on the clotting mechanism

Absence of other pharmacodynamic effects Pyridinolcarbamate was practically devoid of neuropharmacologic cardiovascular autonomic and smooth muscle effects in the pharmacologic doses utilized in our studies.

Assay of drug in biologic fluids A 2-ml portion of whole blood or urine was added to 10 ml of methanol and centrifuged The precipitate was extracted twice with 10 ml of methanol The extract was then evaporated in vacuo to dryness and the residue was dissolved in a mixture of 10 ml of 0 45 per cent $ZnSO_4$ and 2 ml of 0 1 N NaOH by heating Any remaining insoluble material was filtered off immediately The filtrate was alkalinized with 2 ml of 0 1 N NaOH and extracted four times with an equal volume of chloroform The chloroform extract was evaporated in vacuo to dryness and the residue was dissolved in 1 or 2 ml of distilled water by heating After the insoluble material had been filtered off the optical density at 264 mμ was determined The concentration of pyridinolcarbamate in the blood or urine was calculated by use of the standard curve.

Absorption of pyridinolcarbamate from the gastrointestinal tract takes place rapidly in man and animals. In m— -

dose of 0.5 Gm. gives a maximal blood level amounting to 31.3 to 34.0 μg per milliliter within 3 to 6 hours and a dose of 1 Gm. will give a maximal blood level of 52 to 56.3 μg per milliliter. A blood concentration exceeding 10 μg per milliliter is maintained from 16 to 24 hours. Pyridinolcarbamate is excreted mainly in the urine and feces. Thirty to 51 per cent of pyridinolcarbamate given by mouth was recovered from the urine within 48 hours.

Clinical studies

Methods and materials. Ninety patients (see Table I) who were selected from the medical wards of the university hospital participated in this study. Although there is no established indication for bradykinin antagonist, the authors selected patients who were suffering from (1) ischemic disease processes, such as the coronary heart diseases, (2) systemic inflammatory states, (3) purpuric states, and (4) painful disease states.

GROUP 1. ARTERIOSCLEROTIC HEART DISEASE AND ANGINA PECTORIS. Thirty patients with well-documented arteriosclerotic heart disease and angina pectoris were the subjects of this study. Fifteen were males and 15 were females. The age range was from 42 to 74 years, and the duration of the angina pectoris was 4 to 8 years in 8 patients, 1 to 3 years in 10 patients, and 2 months to 1 year in 12 patients. Nineteen patients suffered from angina pectoris on selected exertion or during violent emotions. Eleven patients suffered from angina pectoris with slight exertion or excitement; some attacks occurred spontaneously at rest. One patient with angina at rest in the early morning hours showed typical electrocardiographic features of a variant form of angina pectoris described by Prinzmetal and associates.[11] All patients were symptomatically relieved by sublingual nitroglycerin, except the last mentioned patient with a variant form of angina in whom nitroglycerin was ineffective. Associated disease states included hypertension (3 patients), diabetes mellitus (3 patients), and arteriosclerotic aortic insufficiency (1 patient). After the patients were admitted to the hospital, placebo medication was started immediately for the first 2 weeks. Thereafter, either placebo or pyridinolcarbamate was administered by a double-blind technique. At the end of every 10 to 14 days the double-blind study was replaced by the administration of either placebo or pyridinolcarbamate for another 10 days or 2 weeks. The intensity, duration, quality, and frequency of anginal attacks were described every day by attending physicians.

Master's two-step test.[12] A separate study was performed on selected angina patients at the end of each period of placebo and pyridinolcarbamate. Three hours before performance of the Master test, either pyridinolcarbamate or placebo was administered by the double-blind technique. In 9 patients the first test was performed after placebo and the second test after pyridinolcarbamate. In the other 11 patients the first test was performed after pyridinolcarbamate and the second test

Table I

Disease state	Number of patients: Treated	Number of patients: Improved
A. Ischemic disease conditions		
Angina pectoris	30	25
Arrhythmias	9	6(2*)
B. Inflammatory conditions		
Rheumatic fever	4	4
Rheumatoid arthritis	11	6
Herpes zoster	1	1
Viral hepatitis	8	0
Chronic nephritis	6	0(1*)
C. Purpuric states		
Allergic purpura	7	6
Idiopathic thrombocytopenic purpura	3	3
Banti's syndrome with capillary fragility	1	1
D. Severe painful states		
Trigeminal neuralgia	2	2
Vascular neck pain (Takayasu's disease)	1	1
Cancer pain (stomach cancer)	1	1
Hemicrania	6	2
	90	

*Capillary fragility.

after placebo. Special hematologic studies were also carried out. Prior to and at 1, 10, and 30 minutes after administration of placebo or pyridinolcarbamate the adhesive platelet count was obtained by the modified Moolten Vroman[22] method of Sano, and the one-stage prothrombin time with Thrombokinase*[19] was determined. Twenty subjects with angina pe...

...to 48 years. (5) Chronic nephritis with moderate albuminuria and hematuria—6 patients who ranged in age from 28 to 67 years.

GROUP 3. Purpuric states. Four male and 3 female patients had allergic purpura ranging from 1 to 4 months. The age range of these patients was 28 to 58 years. The 3 female patients, 18, 36, and 52 years old, had idiopathic thrombocytopenic purpura. The 18-year-old patient had severe recurrent menstrual bleeding despite steroid therapy. One male patient, 36 years old, had splenomegaly, thrombocytopenia, and petechiae.

GROUP 4. Severe painful organic disease states. (1) Two female patients, 56 and 26 years old, had trigeminal neuralgia. (2) A 31-year-old female patient had Takayasu's disease and neck pain. (3) A 59-year-old female patient had cancer of the stomach and abdominal pain. (4) Six patients had hemicrania—2 males and 4 females who ranged in age from 31 to 62 years.

PYRIDINOLCARBAMATE ADMINISTRATION—DOSE AND TIME RELATIONSHIPS. The initial dosage of pyridinolcarbamate was 0.5 to 1.5 Gm. once, twice, or three times daily. The subsequent maintenance dose was titrated according to the individual's response and averaged 1 Gm. per day in the majority of patients. The average period of observation for the entire group was 5 months. Thirty-two patients were evaluated for more than 1 year. Pyridinolcarbamate was supplied in tablets of 100 and 250 mg. by the Banyu Co., Ltd.

Results (see Table I)

Group 1. Angina pectoris. Fig. 1 shows a comparison of the number of anginal attacks that occurred during the placebo and pyridinolcarbamate treatment. The black section of the column represents the number of patients who had anginal attacks every day, the lined section represents the number who had them not every day but several times in every week, and the white section represents those who had almost no attacks. That is, during the placebo treatment 17 (56.7 per cent) of all 30 patients had anginal attacks every day (*left column*), and during the pyridinolcarbamate treatment 4 (13.3 per cent) of all 30 patients experienced the attacks every day (*right column*). This difference is statistically significant ($p < 0.001$). Thirteen patients had the attack not every day but several times in a week during the placebo treatment, whereas 7 others had the attacks every week, and 19 suffered almost no attacks during the pyridinol

*Geigy Ltd., Switzerland.

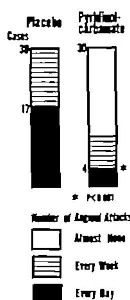


Fig. 1 The number of patients who exhibited the anginal attacks every day (*black section*) or every week (*lined section*) or who had almost none (*white section*). *Note* A statistically significant decrease in the number of anginal attacks ($p < 0.001$) is seen with pyridinolcarbamate as compared with placebo.

carbamate treatment That is the number of attacks was significantly smaller with pyridinolcarbamate therapy than with placebo (Fig 1)

Of the 19 patients with angina pectoris on selective exertion 15 showed definite clinical improvement on pyridinolcarbamate therapy 4 of whom also showed definite electrocardiographic improvement. In the groups which improved on pyridinolcarbamate therapy 11 of the 15 patients relapsed on placebo therapy with 3 showing reappearance of electrocardiographic abnormalities. Ten of the 11 patients with angina at rest showed clinical improvement In the groups which improved on pyridinolcarbamate therapy 11 of the 15 patients relapsed on placebo therapy with 3 showing reappearance of electrocardiographic abnormalities. Ten of the 11 patients with angina at rest showed clinical improvement and 1 patient also showed electrocardiographic improvement. Six of the 8 patients who improved on pyridinolcarbamate suffered a relapse when subsequently placed on placebo therapy All 17 patients who suffered the relapse on placebo therapy were placed again on pyridinolcarbamate treatment and again improved except one In the patients who improved with pyridinolcarbamate the reduction in the frequency of anginal attacks usually occurred on the second or third day of therapy and the improvement persisted for at least 2 to 3 days after cessation of the drug

MASTER'S TWO-STEP This test[20] was performed by 20 subjects with proved arteriosclerotic heart disease and angina pectoris. Three hours after placebo medication the exercise test induced an anginal attack in 10 patients, definite ST T depression (over 0 15 mV) in 17 patients, atrial extrasystole in 3 patients ventricular extrasystole in 2 patients and prolongation of the P-Q interval in 1 patient. In the same test performed on these subjects 3 hours after the administration of pyridinolcarbamate, anginal pain occurred in 4 patients, ST T



Fig 2 Exercise ECG induced by the Master two-step test under placebo (*left column*) and pyridinolcarbamate (*right column*) A positive exercise ECG was obtained in 17 (85 per cent) of all 20 patients on placebo and in 11 (55 per cent) of the same 20 patients on pyridinolcarbamate, and this difference is statistically significant ($p < 0.05$) The borderline change (S-T depression less than 0.15 mV) was found in 2 patient (10 per cent) on placebo and in 5 patient (25 per cent) on pyridinolcarbamate, and the negative exercise ECG was found in 1 patient (5 per cent) on placebo and in 4 patient (20 per cent) on pyridinolcarbamat

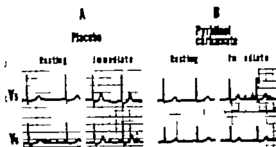


Fig. 3. S.H., a 53-year-old woman. *A*, Exercise test performed 3 hours after taking placebo. Normal resting record and ischemic S-T segment depression in Leads V_{4-6} immediately after exercise. *B*, Exercise test performed 3 hours after taking 1.0 Gm. of pyridinolcarbamate. Normal resting record and negative exercise test.

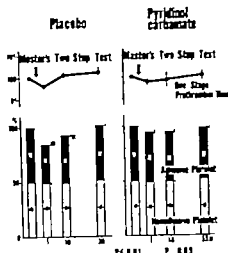


Fig. 4. *Placebo*: Three hours after taking placebo, 18 patients suffering from angina pectoris performed the Master two-step test. Their one-stage prothrombin time (*left upper curve*) and adhesive and nonadhesive platelet count (*black and white columns on the left side*) are described in percentage. A shortening in the one-stage prothrombin time was noted 1 minute after the test ($p < 0.05$) and a reduction in adhesive platelet count was also noted 1 minute and 10 minutes after the test ($p < 0.01$). *Pyridinolcarbamate*: Three hours after taking 1 Gm. of pyridinolcarbamate, the same patients performed the Master two-step test. The one-stage prothrombin time (*upper right curve*) and platelet count (*columns on the right side*) exhibited no significant change.

depression in 7 patients, atrial extrasystole in 2 patients, ventricular extrasystole in 2 patients, and prolongation of the P-Q interval in none. This improvement was statistically significant ($p < 0.05$) (Figs. 2 and 3). In addition, the one-stage prothrombin time and adhesive platelet count were tested prior to and after the Master test. The one-stage prothrombin time was significantly shortened ($p < 0.05$) and the adhesive platelet count was significantly reduced ($p < 0.01$) in the placebo-treated patients. These changes did not occur in the patients treated with pyridinolcarbamate (Fig. 4).

ARRHYTHMIAS. In 2 patients, ventricular extrasystoles persisted during placebo treatment and disappeared with pyridinolcarbamate treatment. The disappearance of extrasystoles occurred 24 and 36 hours after pyridinolcarbamate, respectively, and the effect lasted for 2 and 3 days, respectively, after the discontinuation of the drug. In 1 patient the left bundle branch block was associated with hypertensive cardiac disease, and the arrhythmia disappeared consistently on pyridinolcarbamate treatment and reappeared regularly when the drug was replaced with placebo (Fig. 5). In 1 patient suffering from Stokes-Adams syndrome with bradycardia, pyridinolcarbamate induced a favorable response (Fig. 6). Three of the 4 patients suffering from atrial fibrillation of long duration showed no improvement, whereas in 1 patient with a 12 year history the arrhythmia converted to normal sinus rhythm on the twenty-ninth day of pyridinolcarbamate treatment accompanied by a small cerebral embolus. Fortunately, this latter episode was slight and the patient recovered with only a minimal residual paresis of fingers of the left hand. Normal sinus rhythm has continued to the present time (over 9 months) on a maintenance dose of pyridinolcarbamate. In another patient with a 2-month history, atrial fibrillation disappeared on the second day of treatment with pyridinolcarbamate. Placebo replacement was not possible in the latter patients.

CASE 1. A 71-year-old woman was hospitalized on Nov. 2, 1964, for complaint of palpitation and dyspnea. The abnormal cardiovascular findings were an elevated blood pressure (200/96 mm. Hg), moderate cardiomegaly, slight edema of the lower extremities, and left bundle branch block by ECG and VCG. Serial electrocardiograms were taken twice a day.

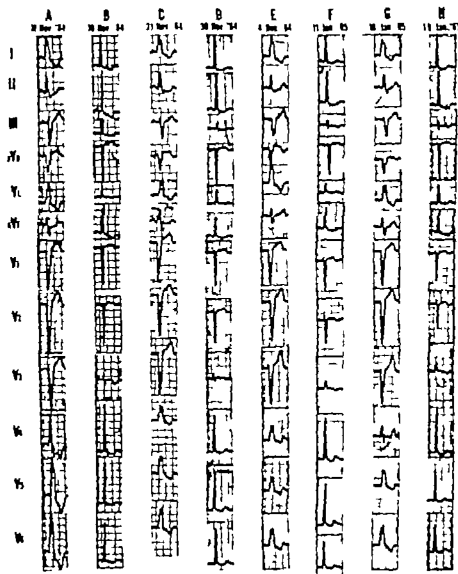


Fig. 5. Case 1. Serial ECG of 71-year-old woman. Her left bundle branch block disappeared when pyridinolcarbamate was administered, and reappeared with placebo.

Immediately after hospitalization, hydrochlorothiazide was given in a daily dose of 50 mg. Within several days the edema disappeared and the blood pressure fell to 180/85 mm. Hg. The abnormal electrocardiogram persisted as shown in Fig. 5,A.

Pyridinolcarbamate was then administered in a daily dose of 1 Gm. On the third day of treatment a normally conducting ECG pattern appeared, intermixed with that of left bundle branch block, and on the fifth day the bundle branch block disappeared (Fig. 5,B). Hydrochlorothiazide was subsequently withdrawn and on the third day after cessation of the drug the left bundle branch block pattern reappeared (Fig. 5,C). Hydrochlorothiazide treatment was reinstituted and the dose of pyridinolcarbamate was increased to 2 Gm. for 3 days, and the left bundle branch block pattern again returned to normal sinus rhythm (Fig. 5,D). Pyridinolcarbamate was then replaced by a placebo, and subsequent serial electrocardiograms revealed burst of left bundle branch block (Fig. 5,E). The patient was again started on pyridinolcarbamate and hydrochlorothiazide and was discharged from the hospital. On January 10 she was again hospitalized. She continued to take pyridinolcarbamate and hydrochlorothiazide and the electrocardiogram showed a normal sinus rhythm (Fig. 5,F). On January 17 pyridinolcarbamate was replaced by placebo. On the second day of placebo the left bundle branch block (Fig. 5,G) reappeared. Replacement of placebo with pyridinolcarbamate was again immediately associated with a reversion of the ECG to normal

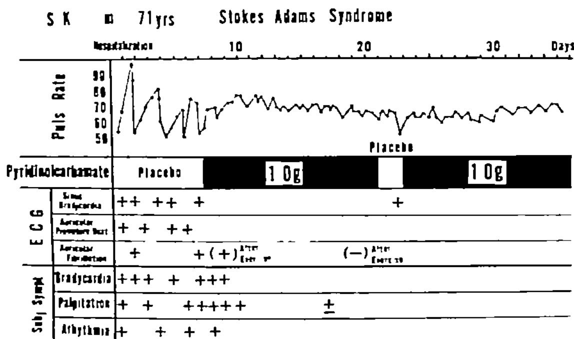


Fig 6 Case 2. A 71-year-old man with Stokes-Adams syndrome The possible beneficial effect of pyridinolcarbamate treatment is seen in his pulse rate, ECG and subjective symptoms.

sinus rhythm (Fig 5,*H*) similar to the earlier experience.

Case 2. In 1962, a 71-year-old clerk had two episodes of unconsciousness lasting approximately 30 seconds. From October 1964, he began noting two to three syncopal attacks per month and frequent episodes of dizziness of a few seconds duration accompanied by bradycardia (Fig 6).

On admission his systolic blood pressure was 164/85 mm. Hg A chest x-ray film revealed no appreciable enlargement of the heart. Laboratory findings, including serum electrolytes and detailed EEG analysis, revealed no appreciable abnormality

After admission he received placebo therapy for 1 week. His heart rate was less than 40 per minute every morning. Paroxysmal atrial fibrillation occurred frequently especially in the morning and sometimes in the afternoon. He complained of dizziness during periods of marked bradycardia. On his seventh day of hospitalization pyridinolcarbamate tablets were substituted for placebo. The following afternoon after he had taken pyridinolcarbamate, the bradycardia subsided and the heart rate increased slowly to 70 per minute with regular sinus rhythm. During the period of pyridinolcarbamate treatment he experienced no attacks of syncope or dizziness. On the eleventh day pyridinolcarbamate was replaced by placebo treatment. On the second day of therapy sinus bradycardia of 48 per minute was recorded. With reinstitution of pyridinolcarbamate the bradycardia again disappeared and he has remained well on pyridinolcarbamate treatment, with no recurrence of arrhythmia or syncope for 13 months.

Group 2 Inflammatory conditions Inflammatory swelling of the joints in 4 patients suffering from rheumatic fever responded promptly to pyridinolcarbamate, disappearing within 12 to 24 hours after 1 Gm of oral pyridinolcarbamate In addition, the fever fell and the antistreptolysin-O titer was significantly lowered within 2 to 4 months after pyridinolcarbamate therapy had been instituted.

In 5 of the 11 patients with definite or classic rheumatoid arthritis pyridinolcarbamate appeared to have no effect however in the other 6 patients it exerted a mild but beneficial effect. There was a significant and rapid reduction in the edematous swelling of joints a definite improvement in morning stiffness and mild relief of pain The fever also fell in 4 of 6 patients. In a 62 year-old patient with complicating steroid diabetes the reduction in the steroid dosage had not been possible without the recurrence of inflammatory swelling of the joints over a period of 3 years With pyridinolcarbamate treatment it was possible to reduce her prednisolone dosage from 6.5 to 3 mg., a result of this reduced requirement

of steroid the patient's steroid diabetes showed marked improvement

One patient suffering from trigeminal herpes zoster with a severe edema of her face and neuralgia responded promptly to pyridinolcarbamate with complete relief of facial edema and trigeminal neuralgia almost 12 hours after administration of the drug After 1 week of treatment the drug was replaced by a placebo and the neuralgia recurred and lasted during the entire period of placebo treatment. Improvement again occurred with initiation of pyridinolcarbamate

All patients suffering from viral hepatitis and chronic nephritis showed a stable but moderate abnormality in their liver or kidney function tests The administration of pyridinolcarbamate in a dose of 1 Gm daily for 1 week to 10 days failed to result in any clinical or laboratory improvement Also no aggravating effect was noted in the clinical and laboratory findings

Group 3 Allergic purpura In 6 of all 7 patients the administration of pyridinolcarbamate in a dose of 1 Gm promptly prevented the formation of petechiae on the second day of treatment

The Rumpel Leede phenomenon became negative on the second day of pyridinolcarbamate treatment in 3 patients and in 1 patient with Banti's syndrome and definitely diminished on the third day in the other 3 patients. During the administration of pyridinolcarbamate no recurrence of the bleeding was observed In 1 patient petechiae recurred during heavy work however the size of the petechiae which appeared was smaller and the number fewer than before pyridinolcarbamate treatment The daily dose of pyridinolcarbamate was increased to 2 Gm and this resulted in complete disappearance of petechiae. Three months after this treatment the drug was withdrawn and there was no recurrence of petechiae for the ensuing 6 months. In 1 patient the administration of 1 Gm of the compound for 10 days failed to show beneficial effect and in 3 patients with idiopathic thrombocytopenic purpura the Rumpel Leede phenomenon became negative on the second day of pyridinolcarbamate treatment The prolonged bleeding time became normal concomitant with subsidence of petechiae On the other hand the reduced platelet counts were not immediately increased by pyridinolcarbamate treatment The examinations of bone marrow revealed no special changes after the administration of pyridinolcarbamate.

In the first patient (Case 3) the drug was replaced by placebo after 4 days of pyridinolcarbamate treatment and within 3 weeks the petechiae reappeared in association with a subarachnoid hemorrhage The bleeding time was prolonged again to 40 minutes and the Rumpel Leede phenomenon again became strongly positive. Reinstitution of pyridinolcarbamate treatment normalized the bleeding time on the second day and the Rumpel Leede phenomenon again became negative. After 1 month of the treatment the platelet count increased slowly to 233 000 Pyridinolcarbamate was again discontinued and the patient remained well without medication for the ensuing 13 months (Fig 7)

The second patient (Case 4) was an 18-year-old woman who developed a severe anemia as a result of repeated severe menstrual bleeding After institution of pyridinolcarbamate no abnormal bleeding was found except for the appearance of a few small petechiae on her arm during the following two menstrual periods.

Menstrual bleeding was normal and her anemia improved without an increase in her platelet count At the end of 3 months, pyridinolcarbamate was replaced by betamethasone in a daily dose of 1.5 mg On the second day of betamethasone treatment many petechiae suddenly appeared on her breast and arm in association with prolonged bleeding time and a positive Rumpel Leede sign On the third day the steroid was replaced by pyridinolcarbamate with subsequent subsidence of petechiae and restoration of abnormal bleeding tests. Two months thereafter her platelet count slowly began to increase to 120 000 and 4 months later her platelet count was 230 000 she has now been well without pyridinolcarbamate treatment for 13 months (Fig 8)

The third patient was a 36-year-old woman who responded promptly to pyridinolcarbamate Her platelet count recovered slowly during 3 weeks of the medication and thereafter no recurrence was observed for 9 months

Another patient (Case 5) a 67 year-old woman was hospitalized in the University

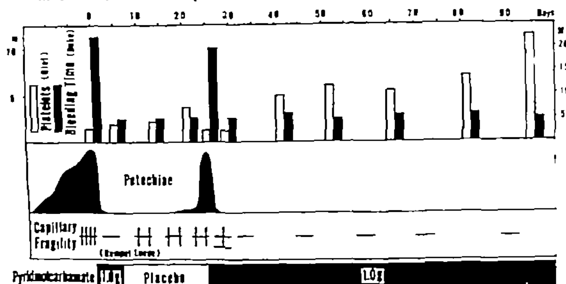


Fig 7 Case 3 A 45-year-old woman with idiopathic thrombocytopenic purpura. The prolonged bleeding time petechiae, and so-called capillary fragility promptly disappeared when pyridinolcarbamate therapy was instituted, reappeared with placebo, and again promptly disappeared with pyridinolcarbamate therapy

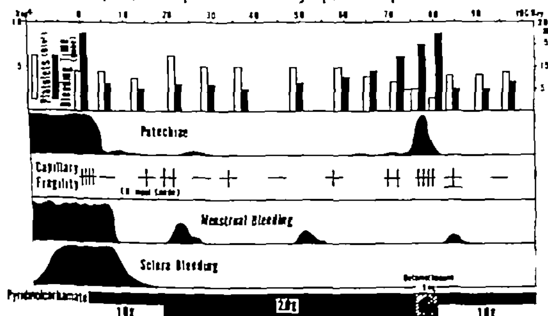


Fig 8 Case 4 An 18-year-old woman with idiopathic thrombocytopenic purpura The prolonged bleeding time, petechiae, so-called capillary fragility prolonged and severe menstrual bleeding, and scleral bleeding promptly disappeared with pyridinolcarbamate therapy When pyridinolcarbamate was replaced by betamethasone the prolongation of the bleeding time and petechiae reappeared and again promptly disappeared yridi carbamate.

Hospital because of gross hematuria and the cystoscopic observation revealed bleeding from both ureters. She was hypertensive (262 100 mm Hg) and was found to have albuminuria and mild azotemia It was thought that she had either an acute exacerbation of chronic nephritis or acute nephritis, and placebo treatment was instituted On the third day of her hospitalization a single 1-Gm dose of pyridinol carbamate was given Six hours later a significant reduction in the bloody appearance of her urine was noted Another 1 Gm was then given and gross hematuria disappeared 12 hours after initiation of pyridinolcarbamate treatment The level of blood urea nitrogen and the blood pressure gradually fell within 2 or 3 days. Nausea and headache also disappeared Pyridinolcarbamate was discontinued after 1 month of treatment Six months later she was well showing no abnormality in her urine

Group 4 Painful conditions A 64-year old man suffering from hemicrania received large doses of aspirin for control of pain Treatment with pyridinolcarbamate did not bring complete relief but it did result in a definite reduction in the number of aspirin tablets required for control of headache In the other 4 men with hemicrania no improvement was found with pyridinolcarbamate A 56-year-old woman with headache associated with a pheochromocytoma showed definite improvement of the headache on pyridinolcarbamate treatment A 56-year-old woman and a 26-year-old woman with several attacks of trigeminal neuralgia a 69-year old woman with severe pain from stomach cancer and a 31 year-old woman suffering from Takayasu s disease with an occlusive arterial change in her left carotid artery were treated with pyridinolcarbamate Their severe pain disappeared promptly within 20 to 30 minutes after a single dose of 0.25 to 1 0 Gm of pyridinolcarbamate and the effect lasted for 4 to 6 hours Placebo therapy did not result in the relief of pain The prolonged euglobulin lysis time of the last-mentioned patient showed a gradual normalization after 2 months on the pyridinolcarbamate treatment

Toxic side effects Slight gastric distress and anorexia were noted in 6 patients, and diarrhea in 3 patients No drug fever rash or toxic effects to blood or liver or the other organs were found in this study

Discussion

A definite antianginal effect of pyridinol carbamate was found by a double-blind technique in this clinical study Similar findings have been reported from several university hospitals in Japan in over 600 cases of angina pectoris. One of the important findings in the study of pyridinol carbamate in patients suffering from angina pectoris was the prevention of clinical hematologic and electrocardiographic changes induced by the Master two-step test [a] Needless to say the evaluation of drugs in such morbid conditions as angina pectoris or arrhythmias is an extremely difficult problem However the clinical and laboratory findings after the exercise test lend objective evidence to the effectiveness of pyridinolcarbamate and suggests the direct effect of pyridinolcarbamate on the anginal attacks. However the clinical improvement due to the drug took place usually 2 to 3 days (sometimes weeks) after the initiation of the therapy and the recurrence of anginal attacks after withdrawal of the medication did not take place immediately but within at least 2 or 3 days thereafter

Such evidences suggest the coexistence of some beneficial effects of pyridinolcarbamate on the pathophysiologic conditions themselves of the heart, which constitute the background and origin of the anginal attacks, such as narrowing of the affected coronary arterial segment by atheromatous plaque.

Exercise induces an increased demand by the myocardium for oxygen and may induce a hypoxic state in the capillaries supplied by the sclerotic coronary arteries A reduction of pH in the hypoxic state is a factor known to activate kinin forming enzymes in the blood as well as to inhibit enzymatic destruction of formed kinins by kinase [1,4,4] As suggested by Burch and DePasquale the release of bradykinin and its active homologues in the hypoxic and acidotic capillaries of the coronary circulation may possibly constrict the regional venous segment and result in a local disturbance of blood flow or the leaking of serous substances including pain producing plasma kinins into the

myocardium. Besides the reduction of pH in the hypoxic states, epinephrine released during exercise may possibly participate in the production of plasma kinins through its protease-activating effect. The leaking of plasma kinins may induce anginal pain as suggested by Burch and DePasquale. Edematous inflammation or regional parts of the myocardium induced by bradykinin may possibly result in arrhythmias and also in the pathophysiologic conditions which enhance the appearance of angina pectoris. It appears to be reasonable to hypothesize that the antagonism of regional kinin induced venous constriction by pyridinolcarbamate in the coronary system as well as in the vasa vasorum system of the coronary arterial wall may be the mechanism by which this drug produces a favorable effect on coronary artery diseases. Also this effect may be involved in the preventive effects of pyridinolcarbamate on Lindner's test[27,31] in animals. On the other hand the coronary vasodilating effect of pyridinolcarbamate shown scarcely with extremely large doses of the drug in dogs and rabbits is difficult to consider as the beneficial effect.

The preventive effect of pyridinolcarbamate on the enhanced blood coagulability and the reduction in adhesive platelet count induced by the Master two-step test[22] may be due to the prevention of leakage from leaking vessels by venoconstriction induced by bradykinin. Majno and Palade[19] clearly demonstrated the destruction of platelets in the endothelial gaps during leakage induced by inflammatory substances. The antithrombotic effect of pyridinolcarbamate may be due to its prevention of the destruction of platelets during leakage and also the prevention of stasis resulting from regional venous constriction. The preventive effect of pyridinolcarbamate on the platelet sticking reaction caused by epinephrine[28,29] may also be a contributing factor.

In the case of nephritis with gross hematuria (Case 5) no trial with a placebo was performed. However, such an effect has been reconfirmed in a number of patients in Japan who were suffering from acute nephritis. Improvement of the cases of allergic purpura, even though the vascular lesions were of long standing, is subject to criticism because of the well-known fact that these cases often undergo a spontaneous remission. However, improvement concomitant with the administration of pyridinolcarbamate was so prompt in all of our patients that a spontaneous remission occurring at that time seems to be unlikely in these cases. A similar immediate effect was observed in the patient with idiopathic thrombocytopenic purpura. Of interest was the fact that the disappearance of petechiae consistently preceded the increase in platelet count. Such observations suggest that an important pathogenetic factor of idiopathic thrombocytopenic purpura, and also of allergic purpura, may be related to a vascular abnormality related to plasma kinins. Similar results in the treatment of purpuric disorders with pyridinolcarbamate have been reported recently in over 200 cases in different university hospitals in Japan.

The therapeutic effect of pyridinolcarbamate in inflammatory conditions (rheumatic fever and rheumatoid arthritis) has been confirmed in a number of other university hospitals of Japan. Such consistent results favor the concept that bradykinin and its active homologues are an important pathogenetic factor leading to these inflammatory conditions. However, the anti-inflammatory response of patients suffering from rheumatoid arthritis was not uniform and some received only partial relief of symptoms. It is noteworthy that the combination of pyridinolcarbamate with other anti-inflammatory agents was of benefit to some patients. One of our patients did well on a combination of pyridinolcarbamate and aspirin without steroids. In another patient, the addition of pyridinolcarbamate seemed to reduce the dose of steroid required and thereby allowed amelioration of the complicating steroid diabetes.

The rapid analgesic effect of pyridinolcarbamate seen in selective painful states may be correlated with the author's experimental finding in rabbits in which pyridinolcarbamate inhibited the pseudo-affective response to bradykinin.

The preventive effects of pyridinolcarbamate and its analogues on venoconstriction and venous leakage from an excess of plasmal kinins may explain the beneficial effects of the drug on certain morbid conditions presented in this study. Pyridinol

carbamate may also prevent vascular leakage of substances of high molecular weight, such as enzymes. If such leakage were to occur under the influence of excess kinins local tissue damage and destruction would occur. Such pathologic alterations may be a factor in such biologic processes as aging and arteriosclerosis. The preventive effect of pyridinolcarbamate on atherosclerosis as demonstrated by the author in cholesterol-fed rabbits may support such a hypothesis. The mechanism responsible for the clinical effect of drugs cannot always be explained by a single hypothesis; however, the evidences obtained in the present clinical study of pyridinolcarbamate warrant further clinical investigation.

Summary

Pyridinolcarbamate (2,6-bis(hydroxymethyl)pyridine bis(N-methylcarbamate) is a nontoxic and weak basic synthetic compound. It exhibits a competitive antagonistic effect against venous constriction induced by bradykinin and lysylbradykinin in a number of in vitro and in vivo animal preparations. The specific antagonistic effect appears to be the prevention of leakage from leaking vessels and of the emigration of leukocytes induced by these kinins. In our studies pyridinolcarbamate did not inhibit the effect of bradykinin in the smooth muscle of rat uterus and guinea pig bronchus and intestine unless large doses were used. Pyridinolcarbamate produced a definite but mild anti-inflammatory effect in the usual laboratory models of inflammation. Particularly striking was the preventive effect of this drug on the inflammatory response produced by passive cutaneous anaphylaxis and on the edematous arterial reaction[20, 21] induced by chemical and traumatic stress. The enhancement of blood coagulability induced by this type of stress was also prevented by pyridinolcarbamate. It was also shown to exhibit an antithrombotic and antiatherosclerotic effect in rabbits. Given orally in a dose of 5 mg. kilogram the drug inhibited the appearance of atheromatous change and the accumulation of cholesterol in the arterial walls of rabbits kept on a high-cholesterol diet for 15 weeks. It also prevented the development of electrocardiographic signs of ischemia induced by vasopressin in rats.[22,23] The drug also exhibited a specific preventive effect against the pseudoaffective response induced by bradykinin[22] in animals.

Some of the clinical trials with pyridinol carbamate appeared to hold promise. Given orally in doses of 10 to 30 mg. per kilogram per day, the drug was well tolerated and showed no toxicity. Peak levels in the blood were obtained within 3 to 7 hours, and an effective level was maintained for 5 to 24 hours. The drug was in large part excreted unchanged in the urine. There was no evidence of a cumulative effect, but the metabolic fate of the drug is uncertain at the present stage of investigation.

Ninety patients hospitalized in the author's university hospital have been treated with pyridinolcarbamate. The dose ranged from 0.5 to 2 Gm. per day, with the majority of patients receiving 1 Gm. daily. In addition, well over a thousand patients have been treated with this drug in other hospitals in Japan.

The cumulative clinical experience to data might be summarized as follows:

1. Pyridinolcarbamate exhibited a definite antianginal effect in 25 of 30 patients studied by a double-blind technique. Seventeen of the 25 patients who improved on pyridinolcarbamate showed a relapse when subsequently placed on placebo therapy and again improved on the second course of pyridinolcarbamate therapy except one. The effect usually occurred from 2 to 3 days after the initiation of the therapy and the patient remained improved for at least 2 to 3 days after cessation of the drug. A Master two-step test was performed by 20 patients with angina pectoris (17 suffering from angina pectoris on selective exertion and 3 suffering from angina pectoris on slight exertion). Reduction in the one-stage prothrombin time and the Moolten Vroman's adhesive platelet count was regularly observed with placebo treatment but was effectively prevented by pretreatment of patients with 1 Gm. of pyridinolcarbamate given 3 hours before the test. The S-T depression, anginal pain, and arrhythmia seen with this test under placebo treatment were also significantly inhibited by pyridinolcarbamate pretreatment ($p < 0.01$-0.05).

Four patients with arteriosclerotic heart disease complicated by either ventricular

extrasystole left bundle branch block or Stokes-Adams syndrome induced by severe sinus bradycardia with atrial fibrillation were treated with pyridinolcarbamate. The arrhythmia consistently subsided with drug treatment and subsequently reappeared on placebo treatment. Two of 4 patients with arteriosclerotic heart disease and atrial fibrillation did not respond to pyridinolcarbamate but the other 2 patients, one with a 2 month history and the other a 13-year history of atrial fibrillation responded to the medication with restoration of a normal sinus mechanism.

2. Among the inflammatory conditions treated with this drug neither beneficial effect nor aggravating effect was found in 5 patients suffering from chronic nephritis and in 8 patients suffering from viral hepatitis. Gross hematuria in a patient with an acute exacerbation of chronic nephritis appeared to subside 12 hours after pyridinolcarbamate therapy and the patient subsequently recovered 1 month later.

In all 4 patients with rheumatic fever the edematous swelling of the joints rapidly subsided 24 hours after the administration of pyridinolcarbamate. The fever and the enlargement of the heart improved slowly and the elevated antistreptolysin-O titer was normalized after 2 to 4 months of the treatment.

Six of 11 patients suffering from rheumatoid arthritis experienced no effect from placebo medication, but the substitution of pyridinolcarbamate resulted in a definite improvement in the edematous swelling of the joints, a disappearance or definite improvement of morning stiffness, and a reduction in pain and fever. Treatment in a patient who had required relatively high doses of prednisolone for a prolonged period resulted in a significant reduction in steroids and almost abolished her steroid diabetes.

3. In 6 of all 7 patients suffering from allergic purpura and in 3 patients with relatively severe idiopathic thrombocytopenic purpura, rapid improvement occurred with pyridinolcarbamate treatment. In 1 patient with Banti's syndrome with thrombocytopenia the Rumpel Leede phenomenon promptly became negative after pyridinolcarbamate. The effect was observed 12 hours to 3 days after the medication was given and lasted during the course of medication. All patients appeared to recover completely after 2 to 5 months of the medication. In patients with idiopathic thrombocytopenic purpura, improvement consistently preceded the increase in the platelet count.

4. Although pyridinolcarbamate does not exhibit a specific analgesic effect it was found occasionally to produce in selective cases a rapid amelioration of painful conditions, as seen in six variously morbid conditions, such as trigeminal neuralgia, hemicrania, Takayasu's disease, and stomach cancer.

The authors' preliminary clinical experience with pyridinolcarbamate, a bradykinin antagonist in veins, appears to warrant further clinical trials with this medication.

Addendum

Since this paper was submitted for publication pyridinolcarbamate treatment of atheroma produced by cholesterol feeding in rabbits has been performed successfully. In the course of treatment with daily administration of 10 mg. per kilogram of this compound by mouth for 10 to 15 weeks the edematous feature disappeared from the atheromatous lesions, and the atheromatous mass was rapidly replaced by regenerated smooth muscle fibers. In addition the hyalinized and necrotic foci as well as foam cells, have almost completely disappeared.

In the treatment of 51 patients suffering from arteriosclerosis obliterans, this compound in a daily dose of 1 Gm. exhibited a definite effect in reopening mainly partially but also completely the occluded arterial segments as was shown clearly by arteriography. This curative effect on atherosclerotic lesions has resulted in rapid clinical improvement including the reappearance of absent peripheral arterial pulsations in the majority of patients within 1 to 11 weeks and in some cases after 21 weeks of treatment.

These results have also suggested that treatment with this compound of coronary sclerosis with angina should be on a long term basis as in the case of chemotherapy of tuberculosis with INH.

Perhaps also worthy of note in patients

treated with this compound are the dramatic and sustained disappearance of cerebral bleeding in all 3 patients who were suffering from cerebral arteriovenous anomaly and the disappearance of the red coloration of the nose in all 5 patients suffering from rosacea

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Problems and complications with the use of side-hole cardiac catheters

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When Forssman catheterized himself in 1928[1] he used a "well greased urethral catheter. Since then, in order to improve the facility and safety of intravascular catheterization, a variety of catheters of different designs have been fabricated.

One such modification was the incorporation of holes in the side of the catheter near its tip. The purpose of such side-hole catheters is to (1) permit sampling or adequate recording of pressure when the tip is against the wall of a vessel or chamber and (2) permit rapid and wide dispersion of contrast medium and minimize catheter recoil during the injection of contrast medium. Although the side holes usually serve these intended purposes, they may cause several problems and complications. Some of these problems and the suggested methods for obviating them will be presented in this report.

Artifacts in pressure tracings. Although the side holes near the tip of the catheter prevent complete damping of the pressure tracing when the end hole becomes obstructed, they may result in erroneous pressure tracings under certain circumstances. When a catheter is advanced or withdrawn slowly across a cardiac valve or septum, a point can be reached at which some of the lateral pressure holes are exposed to pressures in one chamber while other side holes or the end hole are exposed to pressures in the adjacent chamber. Under these circumstances the pressure recorded by the manometer will be an artifactual average pressure somewhere between the actual pressures in the two chambers. A left atrial pressure recorded at the time of transseptal catheterization might be considerably reduced by this technique if some of the lateral taps are still in the right atrium, or the recorded left ventricular systolic pressure might be incorrectly low in a patient with aortic stenosis if the openings of the transseptal catheter are simultaneously sensing pres-

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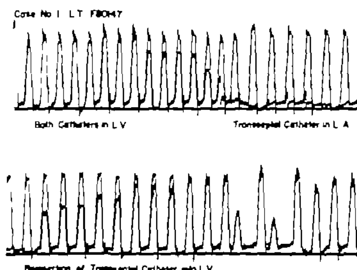


Fig. 1. Simultaneous pressure tracings from a No. 8 Lehman catheter passed retrogradely into the left ventricle and a Brockenbrough catheter passed transseptally into the left atrium and across the mitral valve into the left ventricle. In the upper tracing the Brockenbrough catheter is slowly withdrawn into the left atrium. In the mid-portion of the upper tracing note the false interventricular gradient when some of the side holes simultaneously sense left atrial and ventricular pressures. At the far right of the upper tracing true left atrial pressure is recorded. In the lower tracing the same sequence is repeated as the left atrial catheter is advanced into the left ventricle.

sures in the left ventricle and left atrium (Fig. 1). This phenomenon can be reproduced readily each time that a side hole catheter is slowly withdrawn from the left ventricle to the left atrium across the mitral valve or from the left atrium to the right atrium. Slow pullbacks accentuate this phenomenon; rapid withdrawals minimize or obscure it. If this potential difficulty is anticipated, the artifact can be avoided by making sure that all pressure taps are in the same chamber (i.e., the left ventricle).

Difficulties associated with contrast injections. Several difficulties have arisen during the injection of contrast material. First, in the same manner in which pressure artifacts can be recorded, the injection of contrast material may occur with the side holes located on both sides of a cardiac valve or septum. In this instance two chambers will be simultaneously opacified. Such an occurrence might be incorrectly interpreted as indicating the presence of valvular insufficiency or a septal defect (Fig. 2). One of the side holes may be located in that portion of the catheter which is traversing the atrial septum. With the injection of contrast material not only is the dye delivered into the desired chamber, but a portion may be injected into the wall of the atrial septum itself (Fig. 3). Under other circumstances the end hole might be embedded in the myocardium and the pressure trace appear to be normal. However, with injection of contrast medium the ventricle could be perforated or stained.[7,8] Use of a power injector to deliver the contrast medium under such circumstances might be particularly serious. All of the above-mentioned difficulties can be avoided by proper positioning of the catheter prior to injection. The injection of several milliliters of contrast medium by hand while observing the fluoroscopy screen and electrocardiogram will forewarn the operator of this potential complication.

Side-hole catheters may have either an open or a closed end. The type of catheter with the occluded end has presented a special type of problem with contrast injection. During the period of power injection, the forward force of the injection may be transmitted directly to the sealed tip of the catheter and actually drive the end of the catheter into or through the myocardium and result in myocardial

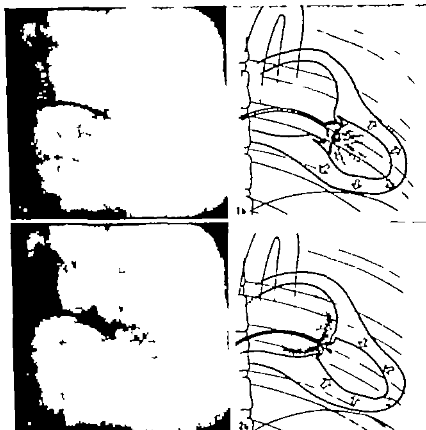


Fig. 2 Selective injection of contrast into the left ventricle via a Brockenbrough catheter passed from the left atrium into the left ventricle. Note that during systole (2a and 2b) the contrast material is being injected into the left atrium simulating systolic opacification of the left atrium due to mitral insufficiency

"staining" or perforation of the heart with injection into the pericardial sac.[4,7] This particular difficulty may be minimized by removing the excess slack from the catheter thereby preventing forward movement of the catheter during the injection.

Catheter insertion and manipulation When side hole catheters are inserted by the percutaneous method it is necessary to pass the catheter through the skin and into the lumen of a vessel over a guide wire. The introduction of side holes weakens the tensile strength of the catheter itself. We have encountered a greater incidence of catheter "buckling" or breaking at the time of percutaneous insertion of side-hole catheters. A partial break in the tip of the catheter may not be appreciated and the catheter may be passed through the interatrial septum into the left atrium over the transeptal needle. Manipulation of the catheter in the left atrium could accentuate the break making easy withdrawal into the right atrium impossible

When side-hole catheters are used in transeptal punctures of the interatrial septum another potential problem exists. When the transeptal needle is advanced for puncture of the interatrial septum as previously reported from this laboratory it is possible for the needle to protrude through one of the side holes rather than through the end hole of the guiding catheter. Despite successful puncture of the interatrial septum by the needle, attempts to pass the catheter over the transeptal needle would be unsuccessful. This complication can be avoided by using catheters in which no side holes are located along the convex curvature of the catheter

Both of these complications can be

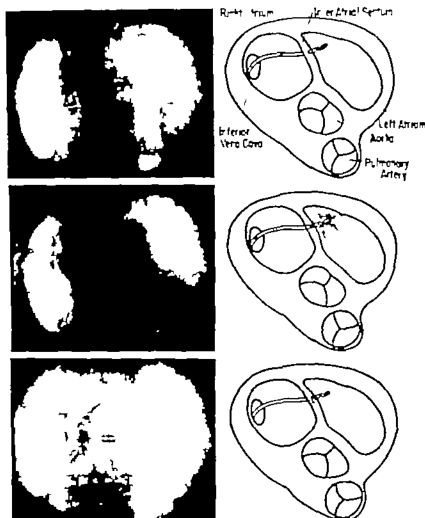


Fig. 3. Selective injection of contrast into the left atrium via a Brockenbrough catheter passed transseptally into the left atrium. Three 35-mm. frames from a cineangiocardiogram are shown on the left. The line drawings at the right show the position of the catheter and the heart from the horizontal plane. In the upper frame the catheter is across the septum and into the left atrium where undamped pressures are recorded but note in the line drawing that one of the side holes is still within the interatrial septum and two are in the left atrium. In the middle sequence the left atrium is fully opacified and is the atrial septum but this is not evident. In the lower frame taken 3 minutes after the injection residual contrast material is seen within the atrial septum. No clinical or electrocardiographic changes were evident, and the staining had completely disappeared by 15 minutes.

either avoided or immediately recognized if one is forewarned that they may arise. A frayed catheter or a transseptal needle protruding through one of the side holes of the catheter can be recognized with a good image intensification radiographic unit. When this occurs the needle should be withdrawn immediately and the catheter replaced before the study is continued.

Another problem which we have encountered with the use of side hole catheters is illustrated in Fig. 4. After transseptal puncture and passage of the catheter into the left atrium the pressure recorded in Fig. 4,A was obtained. There was strong clinical evidence to suspect mild mitral stenosis, but as is shown in the tracing no diastolic gradient was evident. Aspiration with the catheter yielded fully oxygenated blood. To check the position of the catheter a small injection of indicator (indocyanine) was made

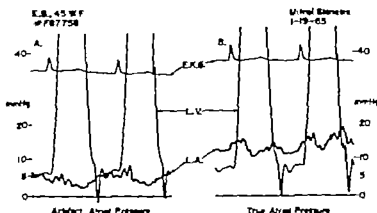


Fig. 4. Pressure tracings from the left ventricle (*L.V.*) and the left atrium (*L.A.*) and the electrocardiogram (*E.K.G.*) in a patient with mild mitral stenosis. Panel *A* shows no diastolic gradient across the mitral valve, and relatively normal contour. Some of the pressure taps of the catheter are sensing pericardial pressure. Panel *B* shows the catheter drawn back within the left atrium and the "true" diastolic gradient is evident.

at this time. No appearance of the indicator was noted at a peripheral artery sampling site. The catheter was slowly withdrawn and finally the pressure tracing shown in Fig. 4,*B* was obtained. A definite mitral diastolic gradient was then present. It was assumed that the tip of the catheter was in the pericardial sac initially and that the side holes were located within the left atrium, thus accounting for the ability to draw blood and yet record a falsely low left atrial pressure. During the injection of the indicator the catheter openings must have been entirely in the pericardial space. The patient experienced only mild discomfort during the entire procedure, but myocardial perforation with hemopericardium was clinically suspected and treated expectantly. At cardiac surgery 10 days later this was confirmed when 50 c.c. of bloody pericardial effusion was found. The important lesson is that the negative or damped pressure characteristic of myocardial perforation was not present, and secondly, a false sense of security was created by the aspiration of what appeared to be fully oxygenated blood. Such a sequence can be recognized by using an indicator to check the position of the catheter and by being aware that almost normal pressure tracings can be obtained with side hole catheters despite the extracardiac location of the tip of the catheter.

Small deposits of fibrin may form at the tip of a cardiac catheter but the presence of side holes may not make this immediately evident since undamped pressures may be obtained. It would appear that such deposits are more common in open-tipped side-hole catheters despite frequent flushing with heparin-saline solution. This frequent occurrence is probably due to the design of the catheter. The presence of an end hole and side holes allows for the flow of fluid from the end hole into the catheter and out the lateral taps, despite the presence of a closed catheter system filled with the anticoagulant mixture. We have observed several instances in which undamped pressures have been recorded but with hand injection of contrast material only the lateral taps were patent. Removal of the catheter has shown a deposit of fibrin occluding the distal tip. It is obvious that this material may be dislodged during manipulation of power injection, and the catheter must be immediately removed.

Summary and conclusions

End-hole catheters have certain disadvantages. Recoil during power injections, frequent damping of the pressure tracing, and difficulty in drawing samples of blood from certain cardiac chambers all have been previously noted. Side-hole catheters overcome all of these technical difficulties. However, these catheters pre-

sent particular problems due to their construction Because the side holes are spaced over a distance of several millimeters from the tip of the catheter pressure gradients may be distorted in the course of pullback recordings, and contrast material may be inadvertently injected into two chambers simultaneously or into the substance of the myocardium itself The catheters themselves tend to be more fragile and hence more difficult to introduce percutaneously They may pose special problems during transseptal catheterization Awareness of these potential problems will allow early recognition and prompt attention to potentially dangerous situations.

Side-hole catheters provide distinct advantages in most situations The present discussion is not intended to discourage their use but to alert the operator to problems that may arise Each of these technical problems has occurred frequently enough in our laboratory to warrant close attention in the course of cardiac catheterization with side hole catheters.

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The effects of supine exercise on left ventricular volume in heart disease

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The effect of exercise on cardiac volume has interested investigators for many years. Several have studied the influence of exertion upon total heart volume in healthy subjects by radiographs and the results have been variable for exercise both in the supine and sitting positions [1-5] Determination of total heart volume provides only an indirect estimate of individual chamber volume, however and more complete understanding of the cardiac adaptation to exercise is aided by specific knowledge of changes in left ventricular size Such measurements have become available from animal investigations in recent years. In the anesthetized dog Chapman Baker and Mitchell[6] used an angiographic method and found a decrease in left ventricular end-diastolic and end systolic volumes with electrically induced exercise Rushmer Smith and Franklin[7] found decreases in left ventricular dimensions in the unanesthetized exercising dog and also demonstrated that ventricular emptying was more complete during exercise

These effects of exercise in man have been the subject of two recent investigations. Changes in left ventricular dimensions with exertion were described by Braunwald and his associates [8] In 4 patients, silver clips were sewn to the left ventricle at the time of mitral commissurotomy or closure of an atrial septal defect After convalescence of the patients cineradiographic analysis of the movement of the clips showed average decreases of 6 5 and 5 1 per cent respectively in left ventricular end-systolic and end-diastolic dimensions with exercise Paley and Leonard[9] studied left ventricular end-diastolic volume in 6 normal volunteers by the thermodilution method With exercise which caused more than a twofold increase in the cardiac output stroke volume rose but left ventricular end-diastolic volume did not change. In these patients, more complete emptying occurred from a left ventricle of unchanged diastolic size

The purpose of this report is to describe measurements of left ventricular volume

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changes with exercise in 30 patients with heart disease.

Method

The thermodilution method for estimation of left ventricular volume has been described previously.[10,11] In this study the left ventricle was catheterized by the percutaneous transseptal method from the right femoral vein and the left brachial artery was cannulated with polyethylene tubing. From the right femoral artery a retrograde catheter with a very small bead thermistor* at the tip was positioned just above the aortic valve. Determinations were made in all patients during a steady state at rest and during the fourth through sixth minutes of exercise. Seventeen patients pedaled a bicycle ergometer at a constant rate with the left leg with resting measurements recorded after the foot was positioned on the pedal. The other 13 patients raised and lowered the left leg to a regular count approximately 20 times per minute. Recordings were made of the electrocardiogram and left ventricular and brachial arterial pressures and the cardiac output was measured by indocyanine green dilution. Oxygen consumption was determined in most patients by Scholander analysis of expired air. Multiple thermodilution curves were produced by rapid injections of 5 ml. or rarely 10 ml. of cooled saline into the left ventricle. The changes in the temperature of aortic blood thereby produced were detected by the aortic thermistor (Fig. 1).

By dividing the cardiac output by the heart rate, forward stroke volume (FSV) was determined. From the average downslope characteristics of the thermodilution curves, the ratio of FSV to ventricular end-diastolic volume (EDV) was obtained. Using FSV and this ratio (FSV/EDV), ventricular end-systolic volume (ESV) and the EDV were calculated.[10,11] The formulas are:

(1) $$FSV/EDV = 1 - \frac{Tn + 1}{Tn}$$

where Tn and Tn+1 are differences between the base-line temperature of aortic blood and that found at beats n and n+1 at end-diastole in the thermodilution curve.

(2) $$EDV = \frac{FSV}{FSV/EDV}$$

(3) $$ESV = EDV - FSV$$

In the presence of aortic insufficiency the calculated ESV includes both the aortic regurgitant volume and the true ESV because the indicator contained in the regurgitant volume contributes to the next end-diastolic ventricular concentration of indicator and is treated mathematically as though it had not left the ventricle in the preceding systole. Mitral insufficiency theoretically invalidates the method and no patients with this lesion were studied.

The Teflon catheter employed for left ventricular catheterization is 70 cm. long, has four side holes located within 1.5 cm.

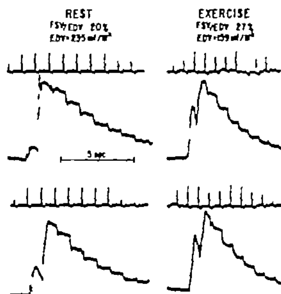


Fig. 1. Duplicate thermodilution curves at rest and during exercise in Patient 9. A decrease in the temperature of aortic blood is shown as an upward deflection. An average ratio of differences in temperature in the downslopes of the curves and a knowledge of stroke volume enabled us to calculate ventricular volume. In this patient who had aortic insufficiency the proportion of the end-diastolic volume ejected as the forward stroke volume averaged 20 per cent in three curves at rest and 27 per cent in three curves obtained during exercise. End-diastolic volume decreased. FSV, Forward stroke volume; EDV, End-diastolic volume. The electrocardiogram is above.

*Victory Engineering Corp., Union, N. J.

of the tip and is size 8½F It was connected to a P23Gb strain gauge* by a 92-cm length of nylon or Teflon tubing with a lumen diameter of 1.85 mm

Thirty patients with sinus rhythm were studied and the diagnoses in each are listed in Table I The subjects presented a wide spectrum of severity of illness. Those with aortic valve prostheses and those who had undergone open commissurotomy for congenital aortic stenosis had few or no symptoms, whereas some with aortic valve disease were severely handicapped No patient had evidence of retention of fluid at the time of the study but congestive failure had been present previously in several Three patients had clinical and angiocardiographic evidence of left ventricular hypertrophy without valvular disease. One of these had mild systemic arterial hypertension and a small systolic pressure gradient across the outflow tract of the left ventricle.

The size of the cardiac silhouette in standard posteroanterior chest radiographs was determined by the method of Schwarz [14] This measurement provides a correction for body size and expresses frontal heart area as a percentage of predicted normal.

Occasionally the exact end-diastolic time for the measurement of pressure in the left ventricle was not apparent from inspection of the record and the pressure 0 05 second after the onset of the QRS complex was used [15]

Results

The complete results are presented in Table I and thermodilution curves from a patient are shown in Fig. 1 The results for volume and flow were corrected for body size and expressed per square meter of body surface area (M²)

The presence of the tip of the transseptal catheter in the left ventricle during exercise did not produce important problems. In some cases, premature beats developed at the onset of exercise but disappeared when the catheter was moved slightly

Evaluation of the method The frontal heart area from chest radiographs was compared with the EDV at rest (ml./M²) The correlation coefficient was 0.73 One patient with right ventricular enlargement due to an atrial septal defect was excluded from this comparison

The reproducibility of the thermodilution curves was appraised in all patients during rest and exercise At rest 111 curves were obtained in the 30 patients, an average per patient of 3 7 curves The downslope function (Tn + 1/Tn) of each curve was compared to the average of downslope functions from all curves in that patient as follows

$$\frac{\left(\text{Average downslope, all curves in patient}\right) - \left(\text{Downslope, individual curve}\right)}{(\text{Average downslope, all curves in patient})} \times 100 = \%\ \text{v}$$

At rest the mean difference of individual curves from the average for the patient in whom they were obtained was 2 4 per cent without respect to sign (S D = 2 3 per cent) With exercise there were 107 curves an average of 3 6 per patient. The mean difference of the downslope function for a given curve from the average for the patient was 3.5 per cent (S D = 3 4 per cent)

The consistency of the exponential downslope of the individual curves was similarly analyzed At rest 387 pairs of downslope temperature "steps" were employed in the calculation of left ventricular volume, each curve providing an average of 3.5 pairs or ratios. The variation of each ratio from the average of downslope ratios for the curve was calculated

$$\frac{\left(\text{Average of downslope ratios for the curve}\right) - \left(\text{Individual downslope ratio of the curve}\right)}{(\text{Average of downslope ratios for the curve})} \times 100 = \%\ \text{va}$$

At rest, the mean difference for a single downslope ratio from the average for the curve was 3 7 per cent, without regard to sign (S D = 3 4 per cent) With exercise there were 401 downslope ratios with an average of 3.8 per curve The mean difference for any individual ratio from the average for the curve was 3 9 per cent without respect to sign (S D = 4.0 per cent)

Marked changes from the ratio of FSV/EDV at rest did not often occur with exercise two of the greatest were from 0.30 to 0 38 in one patient and from 0.20 to 0.27 in another Changes in the EDV were usually in the same direction a

*Statham Transducers, Inc., Hato Rey Puerto Rico.

Table I

Patient	Age (yr.)	Functional class	Heart area by x-ray (% normal)	Electrocardiogram	State	Oxygen consumption (ml./min./M.²)	Heart rate	Cardiac index (L./min./M.²)
Postoperative Aortic Valve Disease								
1	45	1	100	LVH	Rest	120	76	2.28
					Exer	362	92	2. 5
2	5	2	136	ST T	Rest	137	78	3.02
					Exer	331	93	3.79
3	31	1	110	LVH	Rest	137	71	3.70
					Exer	—	85	3.98
4	52	2	110	ST T	Rest	118	76	2.54
					Exer	262	96	4.37
5	18	1	100	Normal	Rest	148	83	3.[illegible]6
					Exer	318	107	4.80
6	13	1	101	LVH	Rest	136	68	2.34
					Exer	392	140	6.00
7	19	1	106	LVH	Rest	152	108	2.96
					Exer	339	120	3.33
Aortic Insufficiency								
8	20	2	125	LVH	Rest	153	78	3.72
					Exer	352	96	3.95
9	51		150	LVH	Rest	170	70	3.27
					Exer	—	83	3.54
10	19	2	165	LVH	Rest	170	77	4.35
					Exer	422	117	5.99
11	41	2	130	LVH	Rest	—	86	2.62
					Exer	—	102	3.18
1	19	1	101	LVH	Rest	159	88	2.77
					Exer	392	100	2.99
13	54	2	136	LVH	Rest	110	68	1.95
					Exer	—	93	3.22
14	37	2	102	LVH	Rest	155	68	2.80
					Exer	359	90	3.10
15	32	1	136	LVH	Rest	154	79	3.42
					Exer	348	114	4.05
16	42	2	133		Rest	157	68	3.69
					Exer	271	84	4.40
17	16	3	148	LVH	Rest	154	81	3.14
					Exer	296	99	3.85
18	22	2	127	LVH	Rest	148	87	3.17
					Exer	—	120	2.88
19	42	2	156	RBBB	Rest	170	78	70
					Exer	333	102	3.14
20	41	2	111	Normal	Rest	154	92	3.68
					Exer	365	108	5.12
Aortic Stenosis and Insufficiency								
21	27	1	110	LVH	Rest	170	78	3.99
					Exer	342	102	4.92
22	30	2	100	LVH	Rest	134	77	3.02
					Exer	—	93	4.19
23	46	3	136	LVH	Rest	—	80	1.49
					Exer	—	92	2.12
24	53	3	127	LVH	Rest	—	66	1.88
					Exer	149	98	2.45

*Cardiac output determined by the Fick principle.

LVH, Left ventricular hypertrophy; *ST-T*, Nonspecific S-T segment and T-wave abnormalities; *RBBB*, Right bundle branch block; *ESV*, End-systolic volume; *CHF*, Congestive heart failure; *TS*, Tricuspid stenosis; *AI*, Aortic insufficiency; *AS*, Aortic stenosis.

In the electrocardiogram, LVH was diagnosed when the R wave in Lead V and the S wave in Lead V or Lead V totaled 35 mm. or

FSV (ml./M²)	EDV (ml./M²)	ESV and regurgitant volume (ml./M²)	FSV / EDV	Pressures (mm. Hg) Left ventricle	Central aorta	Brachial artery	Comments
30	100	70	30	128/4	112/68	120 2	Aortic prosthesis
30	88	58	34	176/7	—	172/94	
39	130	91	30	150/13	—	138/63	Aortic prosthesis
41	108	67	38	192/17	—	194/96	
52	100	48	52	125/8	85 50	95 50	Aortic prosthesis
47	85	38	55	182/18	—	162 80	
33	106	73	31	125 3	110 75	110 70	Aortic prosthesis
46	164	118	28	170/4	—	145 85	
39	115	76	34	127/10	—	142 80	Postoperative AS, slight AI
45	122	77	37	130 5	—	165 85	
34	87	53	39	120 25	90 58	108 58	Postoperative AS, slight AI
43	113	70	38	150/22	—	140 80	
28	165	137	17	148/10	125 80	128 75	Postoperative AS, slight AI
28	140	112	20	160, 10	—	140 85	
48	218	170	22	125 3	—	145 60	
41	172	131	24	145 7	—	185 85	
47	235	188	20	152 19	155 50	165 45	CHF in past
43	159	116	27	175 25	—	185 60	
56	373	317	15	120/17	125 45	168 45	
51	268	217	19	165/16	—	Mean 132	
30	176	146	17	155/26	132/78	142 3	
31	163	132	19	165/25	—	150 80	
31	163	132	19	125/13	120/75	140 70	
30	150	120	20	150 10	—	170 85	
29	181	152	16	175 17	170, 50	180 50	CHF in past
35	167	132	21	215, 21	—	215 65	
41	186	145	22	130 14	130, 60	135 55	CHF in past
34	155	121	22	160 16	—	185 65	
43	187	144	23	118/6	118 60	138 55	
36	190	154	19	175/18	—	200 88	
54	186	132	29	135/11	150 60	150 60	Anemia (hematocrit 28)
52	179	127	29	170/25	—	175 75	
39	216	177	18	125/7	—	Mean 70	
39	216	177	18	145/12	—	—	
36	180	144	20	132/1	110 65	125 65	CHF in past
24	171	147	14	150/8	—	135 60	
35	206	171	17	130, 11	—	140 40	
31	206	175	15	175/12	—	183 65	
40	108	68	37	125/5	125/75	130 70	Slight AI
47	104	57	45	180 16	—	190 90	
51	124	73	41	180, 12	125 78	120, 73	
48	130	82	37	190 15	—	135 80	
39	108	69	36	144/7	96 56	112 54	TS, CHF in past
45	145	100	31	168/6	—	120 76	
19	173	154	11	170, 44	125 60	135 58	CHF in past
23	121	98	19	160 36	—	150 70	
29	116	87	25	230/31	156 68	176 73	CHF in past
27	104	77	26	280, 34	—	270 96	

LAD: Left axis deviation with frontal QRS axis above minus 30 degrees. FSV: Forward stroke volume. EDV: End- [illegible]
ASD: Atrial septal defect.
[illegible] with or without ST-T abnormalities.

Table I —Cont d

Patient	Age (yr.)	Functional class	Heart area by x-ray (% normal)	Electrocardiogram	State	Oxygen consumption (ml./min./M.²)	Heart rate	Cardiac index (L./min./M.²)
Idiopathic Left Ventricular Hypertrophy								
25	14	1	86	LVH	Rest	178	123	4 01
					Exer	297	144	4 50
26.	41	2	100	LAD	Rest	151	103	2 46
					Exer	358	135	2 39
27	41	2	111	LVH	Rest	161	66	2 99
					Exer	313	90	4 14
Miscellaneous								
28.	55	2	130	RVH	Rest	143	98	2 54
					Exer	—	115	3 26
29	44	2	118	P mitrale	Rest	133	72	2 38
					Exer	289	126	2 66
30	20	2	103	Normal	Rest	—	76	4 34
					Exer	287	102	5 56

changes in FSV In the formula for EDV it is apparent that this might be expected since FSV is one of the components in the calculation of EDV However it is emphasized that the calculation of EDV depends *both* on FSV and FSV EDV and that these were independent measurements there were examples in which EDV and FSV varied in opposite directions.

Exercise in patients after aortic valve surgery In terms of physiologic handicap for the left ventricle these 7 patients were the closest to normal of the entire group Studies by indicator-dilution methods from several laboratories have shown the normal EDV at rest probably to be below 135 ml per square meter[9,11,14,17] and in only 1 patient in this group was this value exceeded at rest In 4 patients the EDV fell 12 to 15 per cent with exercise and the ESV also decreased Changes in FSV were variable In the other 3 patients EDV rose with exercise and definite increases in FSV were associated (15 to 39 per cent)

Aortic insufficiency There were 13 patients with aortic insufficiency of varying grades of severity and in 12 of them the EDV at rest was distinctly abnormal. EDV decreased with exercise in 10 patients although in only 4 was the change large The average decrease was 13 per cent (range from 4 to 32 per cent) In general the direction of alteration of FSV and of EDV was similar but 3 patients had a rise in FSV associated with a smaller EDV

Three patients in this group had either no change or an insignificant change in the EDV No patient in the group with aortic insufficiency developed a definite or large increase in EDV with exercise despite the fact that some had severe disease. There was no apparent correlation between the clinical state of disability and the degree of response of the EDV to exercise

The methods employed do not provide a measure of total left ventricular stroke volume when aortic insufficiency is present and thus the true ESV could not be determined in this group

Remaining groups No consistent pattern was observed although there was a tendency for FSV and EDV to vary together The most severely ill patient in the entire study had a decrease in EDV and a rise in FSV with exercise (Patient 23) The 3 patients with idiopathic left ventricular hypertrophy had a decrease in FSV and EDV with exercise

FSV (ml./M²)	EDV (ml./M²)	ESV and regurgitant volume (ml./M²)	FSV/EDV	Pressures (mm Hg) Left ventricle	Central aorta	Brachial artery	Comments
33	137	104	24	115/5	110/85	130/85	
31	103	72	30	125/7	—	150/100	
23	88	65	26	165/16	155/115	165/108	Systemic hypertension
18	60	42	30	190/28	—	200/120	
45	107	62	42	100/7	100/65	120/65	
46	104	58	44	125/12	—	135/85	
26	72	46	36	130/13	—	140/88	Secundum ASD
28	85	57	33	150/25	—	155/85	
33	127	94	26	120/4	—	125/80	Mitral stenosis
21	75	54	28	140/1	—	160/98	
57	139	82	41	100/11	110/70	115/65	Mild mitral stenosis
55	134	79	41	120/12	—	135/80	

End-diastolic volume–end-diastolic pressure relationships. There was no consistent relationship between end-diastolic pressure (EDP) and EDV when patients were compared at rest. Some had a definitely abnormal EDP with a normal EDV.

Changes in EDV and EDP were most often in opposite directions during exercise. The most common pattern was a decrease in EDV associated with an increase in EDP during exertion. In only 9 of the 30 patients did EDV and EDP definitely change in the same direction.

Discussion

Changes in end-diastolic volume with exercise. From animal experiments and previous papers concerning exercise in man we anticipated certain types of responses but did not consistently observe them. We expected that patients with gross cardiomegaly, abnormal EDP and perhaps those with low cardiac output at rest would have further enlargement of the EDV with exercise as has been suggested previously.[4] Instead we often found decreases in EDV with exercise in those with the largest ventricles at rest. Only limited generalization from this point is possible because all those in the present study with the most severe disease had some degree of aortic insufficiency. It is possible that tachycardia and perhaps other factors result in a decrease in the proportion of the stroke volume which regurgitates during exercise and a smaller EDV might occur.[18,19] This explanation is suggested in 7 of the patients with aortic insufficiency who had an increase in FSV/EDV with exercise. The fact remains, however, that EDV decreased with exercise in patients with severe heart disease due to aortic insufficiency, some of whom had had congestive heart failure.

With important aortic insufficiency the ratio FSV/EDV is low and minor variations or errors in the measurement will produce relatively large changes in the calculated EDV for a given FSV (see Formula 2). However, this factor is not believed to be the explanation of the changes in the aforementioned patients since multiple thermodilution curves were analyzed in each patient, because the changes in EDV were reasonably consistent in the aortic insufficiency group, and because the major changes with exercise were of FSV in some patients rather than of FSV/EDV.

In view of past work we anticipated that the postoperative patients without

a gross handicap for the ventricle would have either a decrease in EDV with exercise or no change. Those who had a smaller ESV and EDV with the same or larger FSV with exercise demonstrated this expected normal response with more complete emptying. However, the findings in 3 other patients in the postoperative group and 2 other patients (Patients 22 and 28) suggest that the abnormal heart with a normal EDV at rest may show an increase in the EDV with exercise. If this is the case, a higher FSV will very likely be associated. Whether this response is abnormal is not known, since no patients in the present study could be considered to be entirely free of heart disease.

Other studies of cardiac performance suggest that a larger EDV with exercise need not be abnormal. Occasional increases in left ventricular diameter in the dog during exertion were described by Wilson.[illegible] It also has been shown that FSV may rise remarkably during exercise in healthy people, and it is possible that a normal increase in the proportion of ventricular emptying might not be sufficient to account for the degree of rise observed in FSV. Thus, an increase in EDV would be required. For example, in studies of healthy subjects who exercised in the upright posture to the maximum possible oxygen consumption, Mitchell, Sproule, and Chapman[illegible] found that the average FSV doubled. If the normal left ventricle at rest were 40 to 60 per cent emptied by each systole, which is a reasonable estimate, an increase in EDV would surely be necessary to provide a twofold increase in stroke volume even if ventricular emptying were remarkably complete with exercise. The more complete the emptying at rest, the more likely that EDV would increase with exercise if FSV were to increase greatly. This observation is not entirely analogous to our study, however. Our patients were in the supine position, and the decreases in heart volume and FSV known to occur with assumption of the erect posture provide a different base line for comparison.[illegible] Furthermore, in our patients who had an increased EDV with exercise the increase in FSV was not of such great magnitude. Finally, the level of exercise in our study was considerably short of the maximum oxygen consumption. For the present, however, we have concluded that a normal resting left ventricular EDV which increases with exercise may not constitute an abnormal response when significant increases in FSV are associated.

When consideration is given to the several factors which could influence left ventricular volume, it perhaps is not too surprising that the values found were not more often predictable. These influences might include right ventricular performance, the volume and pressure of the filling reservoir for the left heart, inotropic effects on left ventricular performance, and the impedance to left ventricular outflow. Until more exact means are available for accurately quantifying contractile force of the left ventricle in intact patients, the relative importance of any one of these influences may remain uncertain.

EDP-EDV relationships. The lack of a consistent relationship between left ventricular EDP and EDV is of theoretical interest and practical importance. Published work clearly relates the end-diastolic length of a ventricular muscle segment to EDP in a consistent manner in the dog.[illegible] In addition, the relationship between the length of a segment of left ventricular muscle and EDP is a predictable one when studied at the time of thoracotomy in patients with mitral stenosis and atrial fibrillation.[illegible] Ventricular muscle segment length varies in the same direction with EDV, and therefore a consistent relationship was expected between EDV and EDP. This did not always obtain in our patients during exercise. When EDP and EDV changed in the same direction, our observations were consistent with published experimental data. In most instances, however, EDP and EDV moved in opposite directions, contrary to the concept of a consistent pressure-volume curve for the left ventricle at end-diastole. Several aspects of the exercise response were considered in searching for an explanation.

Marked tachycardia increases the impedance to ventricular filling in the experimental animal, perhaps because of incomplete muscular relaxation.[illegible] Tachycardia has also been found to have this effect in the human heart, but only with

very short diastolic periods, when studied at the time of surgery in patients with mitral stenosis.[29] However the changes in heart rate in our patients were not extreme, and we are forced to conclude that the effects of heart rate alone on the ventricle in diastole do not explain the changes observed

The effects of sympathetic nervous system activity or circulating catecholamines have been reported variously to decrease impedance to ventricular filling [31] not to change diastolic pressure-volume (or muscle segment length) relationships,[32-34] and to increase diastolic left ventricular impedance.[35] In view of these reported variations, it is not possible to conclude with certainty what effects would be expected from these influences in our patients with abnormal hearts.

There have been reports in recent years suggesting that the physical properties of the ventricle are altered by left ventricular hypertrophy The outstanding example is idiopathic hypertrophic subaortic stenosis, in which the left ventricular cavity volume is small, the wall is thick, and left ventricular EDP is often elevated From such findings it has been concluded that the diastolic compliance of the ventricle is reduced resulting in a higher EDP for a given EDV [36-38] The concept of low ventricular compliance helps to explain the lack of correlation of EDP and EDV values obtained in patients at rest However if alterations in compliance alone were involved then consonant changes along this new pressure volume curve with exercise would still occur and this we seldom observed However the compliance characteristics (elastic factors) of the ventricle are not the only determinants of diastolic ventricular pressure as Dodge[39] has pointed out. The resistance components (viscous factors of blood and ventricular wall) are usually overlooked in view of the geometry of the ventricle, the short distance ventricular blood travels in diastole and the large ratio of volume to surface area of the chamber But the resistance component of ventricular muscle may be an important determinant of EDP in some patients, since its effect is proportional to the rate of change in diastolic ventricular volume. It could be postulated that changes in ventricular compliance are associated with forceful atrial contraction when left ventricular hypertrophy is present,[40] and that an accelerated rate of contraction by the left atrium during exercise magnifies the effects of the viscous resistance to left ventricular distention a rate-dependent function. This influence which increases EDP could overshadow the opposite effect on pressure of a smaller volume and thereby produce the results that we found in many patients, a smaller EDV and a higher EDP

Other factors are undoubtedly of importance also It is recognized that the left ventricular pressures that we measured were not the transmural or effective distending pressures since no intrapericardial or intrapleural reference pressure was available It does not seem to us to be likely that changes in intrapleural pressure could account for all of the variability of the changes in EDV EDP relationships but such changes represent an unpredictable, perhaps important factor Alterations in intrapericardial pressure would be especially important if changes in volume of other intrapericardial chambers occurred and the pericardium were not distensible. Work by Rapaport and associates[41] is of considerable interest in this regard They measured right ventricular volumes by thermodilution in patients with heart failure. In five of six instances, right ventricular EDV rose with exercise Intrapericardial pressure could be altered by such changes, thereby altering the measured or absolute left ventricular diastolic pressure in an unpredictable manner

Regardless of the factors responsible we believe that it is evident from our results that the EDV (or muscle fiber length) could not be consistently predicted from the EDP at rest or with exercise in our patients Furthermore the ability of the abnormal left ventricle to change its EDV in a given direction could not be determined from the EDP Thus, we believe that *EDP as routinely measured during cardiac catheterization in man* cannot be used alone as an assessment of the adequacy of the cardiovascular response to exertion by the abnormal heart. It also follows that changes in left atrial pressure or pulmonary capil

lary pressure are not consistently valid reflections of changes in left ventricular EDV

Summary

Left ventricular end-diastolic volume (EDV) was measured by thermodilution in 30 patients with heart disease Those with little physiologic abnormality varied in their response to exertion In some EDV decreased while forward stroke volume (FSV) was maintained or increased In others EDV and FSV rose during exercise

Patients with aortic insufficiency usually had a decrease in EDV with exercise whether FSV increased or decreased In patients with other lesions, FSV and EDV tended to vary together

Changes in EDV and left ventricular end-diastolic pressure with exercise were usually not in the same direction and the factors which may explain this unexpected finding are discussed It is concluded that end-diastolic pressure as usually measured in the left ventricle during cardiac catheterization will not reliably describe EDV or its changes with exercise

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Idiopathic cardiomyopathy
A study of left ventricular function and pulmonary circulation in 15 patients

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In the past 30 years many clinical and pathologic studies of patients with various forms of idiopathic cardiomyopathy have been reported.[1-6] Recently, more extensive clinical, hemodynamic, and angiocardiographic findings in this group of diseases have appeared in the literature.[7-17] On the basis of clinical and laboratory studies, Goodwin, Braunwald, and their respective associates[14,17] have proposed the following classification: (a) minimal or no hemodynamic changes, (b) obstructive pattern (hypertrophic subaortic stenosis), (c) restrictive pattern simulating constrictive pericarditis, and (d) congestive pattern manifested usually by both left and right ventricular decompensation. In a recent review we have discussed in detail the hemodynamic features of these patterns.[11] It was emphasized that the foregoing classification is merely descriptive and not entirely specific. Hemodynamic changes characteristic of more than one pattern may be frequently found in a single patient, and it is possible that one pattern may evolve into another.

Limited information is available in regard to the hemodynamic findings in the left heart in patients with idiopathic cardiomyopathy but with no ventricular outflow obstruction. When studied, some of these patients show little abnormality, whereas others manifest principally either congestive or restrictive features. In some patients with congestive cardiomyopathy, the left ventricle shows significant dysfunction, yet the right ventricle may function normally. This emphasizes the importance and necessity of studying left ventricular performance in these patients.

It is the purpose of the present report to describe the hemodynamic changes in a series of 15 cases of idiopathic cardiomyopathy without ventricular outflow obstruction. There was no evidence of associated systemic disease in any of the patients studied. On the basis of clini-

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cal and hemodynamic findings they are divided into three groups (a) a compensated group including 6 patients without cardiac decompensation or obstruction to blood flow (b) a congestive group of 6 patients with predominantly left ventricular decompensation and (c) a group of 3 patients with restrictive features involving both left and right ventricles. The response to acute digitalization has been studied in some of these patients and these results are included

Material

Compensated group The 6 patients with compensated idiopathic cardiomyopathy ranged in age from 16 to 48 years. All 6 were men and all but 1 (Case 1) had mild exertional dyspnea. None had a history suggestive of cardiac decompensation or coronary artery disease. No patient gave a history of acute rheumatic fever systemic hypertension, chronic alcoholism or malnutrition. A family history of heart disease was absent.

In 4 patients (Cases 1 3 4, and 5) a Grade 1 or 2 ejection systolic murmur was heard at the apex and along the lower left sternal border None had a diastolic murmur elevation of central venous pressure pulmonary congestion hepatomegaly or peripheral edema Clinical, electrocardiographic, and radiologic evidence of left ventricular enlargement was present in all patients. In 3 patients (Cases 3 4 and 5) selective angiocardiograms were obtained which demonstrated abnormal thickness of the left ventricle with a normal or slightly dilated ventricular cavity but no evidence of either valvular disease or subaortic stenosis. At the time of this writing, no patient in this group has had any increase in symptoms or functional disability

Congestive group In this group of patients there were 5 men and 1 woman ranging in age from 28 to 44 years. All patients had a history of exertional dyspnea paroxysmal nocturnal dyspnea weakness and fatigue A familial history of heart disease was noted in 2 patients (Cases 7 and 10) In none of these patients was there a history of rheumatic fever or hypertension One patient (Case 8) had repeated systemic embolization.

A prominent left ventricular impulse was observed in all patients, and a Grade 1 2 apical systolic murmur was demonstrated in all but 1 A Grade 1 2 low pitched apical mid-diastolic rumbling murmur was audible in 1 patient (Case 10) An S_3 gallop rhythm was present in 3 patients (Cases 7 8 and 12) Physical signs of pulmonary congestion were present on admission in 2 (Cases 8 and 12)

Electrocardiographic and radiologic evidence of left ventricular enlargement was demonstrated in all patients In addition fluoroscopy of the chest showed left atrial enlargement in all and probable right ventricular enlargement in 4 (Cases 8 10 11 and 12) Angiocardiographic studies were performed in 2 patients (Cases 11 and 12) and demonstrated an increased thickness of the left ventricular wall but no evidence of specific valvular lesions or outflow obstruction

In Case 10 the initial impression was that of mitral stenosis, and mitral valve surgery was attempted At operation no mitral valve obstruction was found A biopsy of the myocardium showed non specific changes.

Several months to a year after the studies 3 patients died (Cases 7 8 and 11) Postmortem examination of 2 patients (Cases 7 and 11) showed left ventricular hypertrophy moderate right ventricular hypertrophy and absence of valvular lesions or coronary artery disease

Restrictive group Two men and 1 woman had restrictive idiopathic cardiomyopathy They ranged in age from 42 to 57 years. One patient (Case 13) had only mild exertional dyspnea The other 2 (Cases 14 and 15) were severely disabled with marked orthopnea nocturnal dyspnea nonproductive cough and fatigue. In none of these patients was there any demonstrable systemic disease

On admission the jugular venous pressure was elevated and prominent a and v waves as well as rapid x and y descents, were observed in 2 patients (Cases 13 and 14) A soft systolic murmur was heard along the left sternal border and at the apex in each patient An S gallop rhythm was audible in all 3 Hepatomegaly of varying degree was present in all 3 patients and minimal ascites was detected

in 2 (Cases 14 and 15) Pulsus paradoxus was initially observed in 1 patient (Case 15)

Low voltage of the QRS complex in the electrocardiogram and general enlargement of the heart were present in all 3 patients Selective angiocardiography was performed in 2 patients (Cases 13 and 15) and demonstrated enlargement of the left ventricle but no evidence of any valvular lesion or outflow obstruction The right atrial wall shadow was thought to be unusually wide indicating probable pericardial thickening or effusion The possibility of constrictive pericarditis was suspected in 2 patients (Cases 14 and 15) but the diagnosis was not confirmed by exploratory thoracotomy In Case 15 an associated subacute pericarditis was probably present but no definite pericardial constriction was found

Methods of study

Hemodynamic studies were carried out by simultaneous right and transseptal left heart catheterization Right heart catheterization was performed in the usual manner using an antecubital vein Pressures were recorded in the right atrium right ventricle pulmonary artery and pulmonary wedge position The catheter was then positioned in the main pulmonary artery Transseptal left heart catheterization was performed by the technique described by Brockenbrough and associates[19] The left ventricle was entered in all but 2 patients (Cases 9 and 10) A No 18 gauge Cournand needle was inserted into a systemic artery for sampling arterial blood and recording arterial pressure Left ventricular systemic arterial and pulmonary arterial pressures were measured simultaneously In selected patients the first derivative of left ventricular systolic pressure was measured as described in a previous paper[20]

With the two catheters placed respectively in the pulmonary artery and left atrium (or left ventricle) cardiac output was determined by both the Fick procedure and indicator-dilution technique as described elsewhere[20,21]

The methods for computing central blood volume and pulmonary blood volume have been described previously[22,23] The "central blood volume is defined as the amount of blood estimated between the main pulmonary artery and a systemic artery including all equidistant branches of the aorta The pulmonary blood volume is defined as the amount of blood estimated in the total pulmonary vascular bed including all the branches of the pulmonary arteries, capillaries, and veins

In 8 patients (Cases 1 4 6 7 8 12 13 and 14) digitalization was achieved by rapid injection through the right heart catheter of either acetyl strophanthidin (0 02 mg per kilogram) or ouabain (0 01 mg per kilogram) Studies were made during the control period and between 15 and 30 minutes after the onset of injection of acetyl strophanthidin or between 30 and 40 minutes after the onset of injection of ouabain None of the 8 patients was given digitalis for at least 1 month prior to the study

Isoproterenol was infused intravenously at a rate of 1 or 2 μg per minute to 3 patients (Cases 3 4 and 5) In each case, hemodynamic studies were made during the control period and 10 minutes after the onset of infusion

Hemodynamic studies were made in 3 patients (Cases 1 2 and 8) during exercise in the supine position by pedaling a bicycle ergometer with the left foot

Ventricular premature beats were deliberately induced in all patients in an attempt to provoke left ventricular outflow obstruction

In none of these patients was a systolic pressure gradient from the left ventricle to the systemic artery provoked during infusion of isoproterenol during exercise or after a ventricular premature contraction Systemic arterial pulse pressure of the postectopic beat was always greater than that of the control beat.

Results

The age and sex of the patient in these three groups and the special studies and examinations made in these patients are presented in Table I

The results of the hemodynamic studies at rest are summarized in Tables II V As shown in Table II in the patients of the compensated group the cardiac index ranged between 2 76 and 4 49 L./min./M.² and the stroke index between 34 and 60

Table I. Special studies and examination in patients with idiopathic cardiomyopathy

Case No.	Age (yr.)	Sex	Angio*	Administration of digitalis†	Remarks
Compensated group					
1	48	M	O	X	
2.	16	M	O	O	
3	19	M	X	O	
4	25	M	X	X	
5.	23	M	X	O	
6	45	M	O	X	
Congestive group					
7	28	M	O	X	Autopsy
8.	37	M	O	X	Died, no autopsy
9	44	M	O	O	
10.	40	M	O	O	Operation
11	30	M	X	O	Autopsy
12	42	F	X	X	
Restrictive group					
13	45	F	X	X	
14.	57	M	O	X	Autopsy
15	42	M	X	O	Autopsy

*Angiocardiogram taken after injection into the left ventricle via retrograde or transseptal route.
†Acetyl strophanthidin, 0.01 mg. per kilogram, or ouabain, 0.01 mg. per kilogram, injected into the pulmonary artery over a period of 10 minutes.
X Performed or given. O Not performed or given.

ml./beat/M.² The arteriovenous oxygen difference varied between 28.1 and 51.7 ml./L. The right atrial mean and right ventricular diastolic pressures were normal. None of the patients had evidence of pulmonary hypertension. The pulmonary wedge mean, left atrial mean, and left ventricular diastolic pressures were within normal limits. No demonstrable pressure gradient was present across any of the four valves. The left ventricular work ranged from 47 to 77 Gm.M./beat/M.² The arterial oxygen saturation was within normal limits in all patients. The values were normal for the "central" blood volume in 6 patients and for the pulmonary blood volume in the 3 patients in whom the determinations were made.

The hemodynamic data in patients of the congested group (Table III) are distinctly different from the data obtained in the compensated group. Both the cardiac and stroke indices were markedly decreased. The arteriovenous oxygen difference in the 5 patients in whom it was determined was also abnormally wide ranging between 54.1 and 83.6 ml. L. In 1 patient no mixed venous blood was obtained but judging from the extremely low cardiac index, the arteriovenous oxygen difference must have been greater than 54.1 ml. L. Two patients (Cases 10 and 11) had an elevated right atrial mean and right ventricular diastolic pressure. Pulmonary hypertension was documented in all but 1 patient (Case 12). The left atrial mean pressure was elevated (> 12 mm. Hg) in all patients and elevation of left ventricular diastolic pressure (> 13 mm. Hg) was observed in the 4 patients in whom the left ventricle was entered. In 4 patients an abnormally prominent a wave was recorded in the left atrial pressure tracing. In all 5 patients in whom the pulmonary artery was catheterized no systolic pressure gradient was demonstrated between the right ventricle and the pulmonary artery. Although no pulmonary arterial pressure was recorded in Case 7, subsequent postmortem examination failed to show any evidence of pulmonary stenosis or other right ventricular outflow obstruc-

Table II Hemodynamic data in patients with compensated idiopathic cardiomyopathy

Case No	BSA	V_{O_2}	$C_{a_{O_2}} - C_{v_{O_2}}$	CI	HR	SI	RA (m)	RV (S/D)
1	2 13	142	51 7	2 76	81	34	3	22/3
2	1 61	155	43 5	3 58	66	54	4	30/4
3	1 82	144	41 0	3 50	75	47	3	—
4	2 00	131	31 1	4 21	85	50	2	27/3
5	1 68	160	35 8	4 49	79	57	5	34/6
6	1 90	115	28 1	4 08	68	60	4	23/5

BSA Body surface area (M²) V_{O_2} Oxygen uptake (ml/min/M² STPD) $C_{a_{O_2}}-C_{v_{O_2}}$ Arteriovenous oxygen difference (ml/L) CI ... PA Pulmonary arterial PW Pulmonary wedge LA Left atrial LV Left ventricular BA Systemic arterial m Mean ... Central blood volume PBV Pulmonary blood volume

Table III Hemodynamic data in patients with congestive type of idiopathic cardiomyopathy

Case No	BSA	V_{O_2}	$C_{a_{O_2}} - C_{v_{O_2}}$	CI	HR	SI	RA (m)	RV (S/D)
7	2 35	–		1 48	78	21	4	56/3
8	1 80	149	64 2	2 32	138	20	3	40/6
9	1 98	145	58 5	2 48	94	26	1	40/5
10	1 99	135	83 6	1 61	64	25	15	65/15
11	1 8	138	81 8	1 68	100	17	8	55/8
12	1 50	113	54 1	2 09	81	26	4	28/4

*Determined by ... curves only
The abbreviations and symbols are identical to those in Table II

Table IV Hemodynamic data in patients with restrictive type of idiopathic cardiomyopathy

Case No	BSA	V_{O_2}	$C_{a_{O_2}} - C_{v_{O_2}}$	CI	HR	SI	RA (m)	RV (S/D)
13	1 45	123	55 6	1 51	71	26	15	31/15
14	1 9	165	89 3	1 85	100	19	20	42/20
15	1 63	190	96 7	1 35	110	12	10	62/13

The abbreviations and symbols are identical to those in Table II

Pressures (mm. Hg)								
PA (*S/D*,*m*)	*PW* (*m*)	*LA* (*m*)	*LV* (*S/D*)	*BA* (*S/D*,*m*)	S_{O_2}	*SW LV*	*CBV*	*PBV*
23/11,15	—	11	133/13	143/94 110	94 5	47	745	—
26/ 8 16	13	10	124/12	146/76, 96	97 3	63	710	—
20/10 15	—	12	105/10	112/95 100	96 4	58	662	307
27/ 7 15	8	8	150/10	159/91 110	96 2	70	625	—
27/ 8 17	13	12	150/12	155/85 105	96 2	77	748	318
24/10 14	5	6	125/10	135/75 100	93 6	77	660	238

Cardiac index (L./min./M²). *H.R.* Heart rate (beats/min.). *S.I.* Stroke index (ml./beat/M²). *RA* Right atrial. *RV* Right ven-
S Systolic. *D* Diastolic. $S_{a_{O_2}}$ Arterial oxygen saturation (%). *SW* Left ventricular stroke work (Gm. M./beat/M²). *CBV*

Pressures (mm. Hg)								
PA (*S/D*,*m*)	*PW* (*m*)	*LA* (*m*)	*LV* (*S/D*)	*BA* (*S/D*,*m*)	S_{O}	*SW L*	*CBV*	*PBV*
—	—	23	120/22	112/80 90	91 4	21	—	—
36/7,26	22	24	131/32	126/94,104	96 0	20	665	354
40/16,25	—	24	—	95/70 78	95 5	20	—	—
62/35 40	—	26	—	155/100 110	94 8	29	792	280
52/18,31	23	31	82/30	95/75,80	91 3	12	735	—
28/10,17	13	15	110/20	115/80,85	—	22	499	285

Pressures (mm. Hg)								
PA (*S/D*,*m*)	*PW* (*m*)	*LA* (*m*)	*LV* (*S/D*)	*BA* (*S/D*,*m*)	S_{O}	*SW*	*CBV*	*PBV*
35/16,22	17	16	120/15	125/85 100	93 5	32	456	205
37/20,27	22	24	68/30	68/42,50	96 0	5	680	310
47/30 40	26	28	100/42	100/75,85	94 3	8	688	284

tion. In the 4 patients in whom the left ventricle was entered, there was no pressure gradient across either the mitral or aortic valve. In Case 10 the presence of mitral or aortic valvular lesions was ruled out at operation, but in Case 9 exclusion of valvular lesions in the left heart was made on clinical grounds alone. The stroke work in all patients was significantly reduced. The arterial oxygen saturation was slightly decreased in 2 patients (Cases and 11). The central blood volume was slightly increased in Cases 10 and 11, and the pulmonary blood volume was higher than normal in Case 8.

Hemodynamic findings in patients with the restrictive type of idiopathic cardiomyopathy are presented in Table IV. All 3 patients had markedly decreased cardiac and stroke indices with wide arteriovenous oxygen differences. In all cases the right atrial mean and right ventricular diastolic pressures were elevated, and there was a distinct diastolic dip followed by a high end-diastolic plateau. In 2 patients (Cases 13 and 14) the diastolic pressure exceeded one third of the systolic pressure in the right ventricle. In all patients there was a slightly exaggerated respiratory variation in the right ventricular end-diastolic and right atrial pressures. Abnormally elevated left ventricular diastolic pressure was recorded in all 3 patients, and a distinct diastolic dip followed by an abrupt plateau was observed in 2 (Cases 14 and 15). In 2 of the 3 patients in this group the difference between the left atrial and right atrial mean pressures was less than 5 mm. Hg. In Case 14 an abnormally low systemic arterial pressure was present. The arterial oxygen saturation was within normal limits in all 3. The stroke work was slightly decreased in 1 (Case 13) and markedly reduced in the other 2 (Cases 14 and 15). The central and pulmonary blood volumes were either within the normal range or slightly lower than normal.

The range and average values of the various hemodynamic parameters in the three groups are presented in Table V.

As shown in Table VI, after acute digitalization in the patients of these three groups, a decrease in heart rate and an increase in stroke index and stroke work were usually observed. In the compensated and the restrictive groups, the changes in the left ventricular diastolic, left atrial mean, and pulmonary arterial pressures were inconsistent and insignificant (Figs. 1 and 2), whereas in the congestive group there was a striking reduction in these pressures (Fig. 3). In general, whenever there was a significant decrease in the left ventricular diastolic and pulmonary ar-

Table V. Summary of the range and average values of pertinent hemodynamic parameters in three groups

Parameter	Normal range	Compensated group		Congestive group		Restrictive group	
		Range	Average	Range	Average	Range	Average
C.I.	2 0-4 80	2 76-4 49	3 77	1 48 2 48	1 94	1 35-1 85	1 58
$C_{a_{O_2}} - C_{\bar{v}_{O_2}}$	4-41	28 1 51 7	38 5	54 1 83 6	68 4	55 6-96 7	80 5
S.I.	34-60	34-60	50	1 - 6	23	12-26	19
RV_D	<5	3-8	5	3-15	7	13-20	16
PA_m	<20	14 17	15	17-40	28	22-40	30
LA_m	<1	6-12	10	15-31	24	16-28	33
LV_D	<13	10-13	11	20-32	26	15-42	29
SW_L	40-80	47 77	65	1 [illegible]9	21	5-32	15
CBV	594 ± 63	6 5- 48	691	479-793	678	456-655	605
PBV	[illegible]31 ± 5	255-318	294	280-354	307	205-310	266

*Mean ± S.D.

The abbreviations and symbols are identical to those in Table II.

Table VI. Responses to acute digitalization in patients with idiopathic cardiomyopathy

Case No.	Periods of study	Vo₂	Ca – CvO₂	CI	H.R.	S.I	Pressures (mm Hg) PA (m)	LA (m)	LV (S/D)	LV dp/dt (% increase)	BA (S/D,m)	Sao₂	SW LV	CBV	PBV
Compensated group															
1	A	139	66 2	2 10	110	19	17	11	126/12	—	137/96 110	92 7	25	746	346
	B	134	55 1	2 43	95	26	16	—	110/ 8	—	126/81 95	91 6	32	564	210
4	A	130	31 1	4 16	86	52	15	8	140/ 8		155/104 122	92 2	76	616	—
	B	110	32 6	3 38	69	49	14	—	160/10	+19	166/110 127	91 1	82	530	—
6	A	115	28 1	4 08	68	60	14	6	125/10		140/90 110	96 2	77	832	—
	B	117	25 8	4 55	63	72	10	7	120/ 8	+21	140/85 105	93 6	100	770	285
Congestive group															
7	A	—	—	1 48*	78	21	—	23	120/20		112/80 90	91 4	21	—	—
	B	—	—	1 68	72	23	—	4	112/ 8	+18	108/80 89	95 6	26	—	—
8	A	148	64 2	2 32	140	17	26	28	120/30		116/92 100	96 2	16	803	371
	B	153	59 5	2 58	120	21	13	5	122/ 4	+28	130/104 120	96 2	33	700	337
12	A	113	54 1	2 09	81	26	24	14	103/25		100/75 80	—	22	499	285
	B	116	44 6	2 60	75	35	18	8	125/15	+38	125/75 85	—	33	519	214
Restrictive group															
14	A	–	55 6	1 86	79	24	24	16	130/14		145/85 105	93 5	31	456	205
	B		59 5	1 71	60	29	21	14	115/13	+25	140/87 107	95 5	38	451	207
15	A		89 3	1 38	100	14	28	27	75/30		68/42 50	94 3	4	568	310
	B	—	—	1 60*	100	16	30	28	88/29	+23	95/65 78	—	9	780	340

*Determined by indicator-dilution curves only.

A: Control. B: Acute digitalization. LV dp/dt: The maximum rate of change of the left ventricular systolic pressure pulses. Other abbreviations and symbols are identical to those [illegible] Table II.

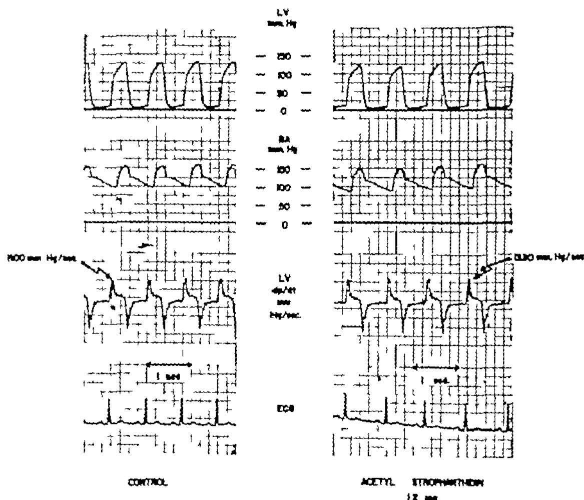


Fig. 1. Effect of acute digitalization in a patient with compensated idiopathic cardiomyopathy. After administration of acetyl strophanthidin there was an increase in dp/dt of the left ventricular (LV) pressure pulse although no significant change in the left ventricular end-diastolic pressure was noted.

terial pressures. A moderate reduction in both central and pulmonary blood volumes was also observed. In all patients in whom the measurements were made there was a definite augmentation of the first derivative of left ventricular systolic pressure (dp/dt), the average increase being about 25 per cent.

Administration of isoproterenol to 3 compensated patients (Cases 3, 4, and 5) failed to induce a systolic pressure gradient across the aortic valve. Cardiac index was determined in 2 patients (Cases 3 and 5) before and during infusion of isoproterenol and the changes were inconsistent. There was, however, an increase in the heart rate in all patients. The changes in the left ventricular diastolic, left atrial mean, and pulmonary arterial mean pressures were not significant. A slight but consistent rise in the left ventricular systolic and systemic arterial pressures was observed.

In no case was a systolic pressure gradient across the aortic valve produced either during administration of digitalis preparation and infusion of isoproterenol or during exercise.[22,23] In all patients the arterial pulse pressure recorded after a premature contraction was always greater than that observed in control beats.[16,17]

Discussion

The diagnosis of idiopathic cardiomyopathy in the patients of the compensated

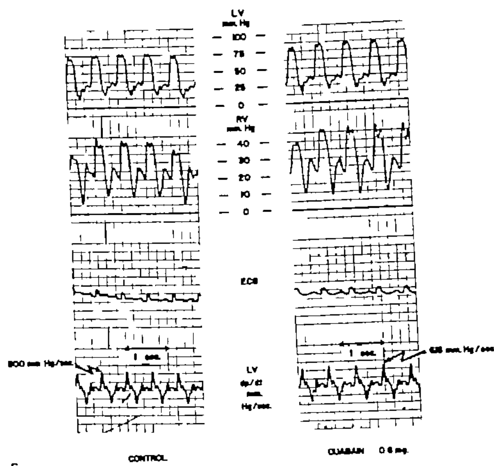


Fig. 2. Effects of acute digitalization in patient with restrictive type of idiopathic cardiomyopathy. Note the diastolic dip-plateau pattern and a prominent "atrial kick" in both left (LV) and right (RV) ventricular pressures. After administration of ouabain there was augmentation of dp/dt of the left ventricular pressure pulse although no change in the left ventricular end-diastolic pressure was observed.

group is based upon the presence of left ventricular hypertrophy, absence of clinical evidence of hypertension or coronary artery disease, and exclusion of known congenital or valvular heart disease by special studies. The hemodynamic findings in these patients closely resemble those described by Braunwald and Aygen.[17] The cardiac index and stroke index were well maintained, the left ventricular stroke work and the pressures in the left ventricle, left atrium, and pulmonary artery were all normal. No features to suggest obstructive lesions, congestive heart failure, or a restrictive process were found.

It is impossible to predict whether patients with compensated idiopathic cardiomyopathy as described in this report will eventually develop left ventricular outflow obstruction, congestive heart failure, or a restrictive process. Each patient in the compensated group has been followed by us for 2 years or more and none has shown any clinical deterioration. Long-term repeated examination of these patients will be required before the natural course of their heart disease becomes apparent.

Based upon clinical, hemodynamic, and angiocardiographic studies, the diagnosis of idiopathic cardiomyopathy in the congestive group seems to be secure in 4 patients (Cases 7, 8, 11, and 12). The diagnosis was further documented by postmortem examination in 2 (Cases 7 and 11).

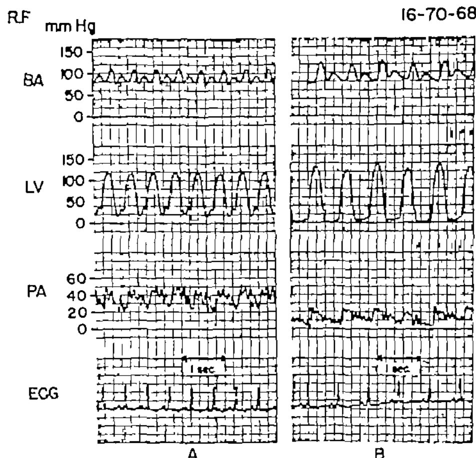


Fig. 3. Effects of acute digitalization on a patient with congestive type of idiopathic cardiomyopathy. After intravenous administration of acetyl strophanthidin there was a significant decrease in both left ventricular (*LV*) end-diastolic and pulmonary arterial (*PA*) pressures.

In Case 10 a tentative diagnosis of mitral stenosis was made because initially neither left ventricular diastolic pressure nor selective angiocardiogram was obtained. In retrospect, it was certain that the patient had idiopathic cardiomyopathy with cardiac decompensation. Other investigators have reported similar experience.[11] In 1 patient (Case 9) the hemodynamic studies were incomplete because of his poor general condition and some technical difficulty during cardiac catheterization; hence the diagnosis of idiopathic cardiomyopathy has not been firmly established.

In sharp contrast to those in the compensated group, all of the patients in the congestive group had a subnormal cardiac index, stroke index, and stroke work associated with an elevated left atrial mean pressure. In 4 patients in whom the left ventricle was catheterized, the diastolic pressure in that chamber was markedly elevated. In Cases 9 and 10 it may be reasonably assumed that there was an increase in the left ventricular diastolic pressure although the left ventricle was not entered. A slight to moderate degree of pulmonary hypertension was present in 5 patients. Furthermore, in Case 10 the right ventricular diastolic pressure was also elevated.

In the compensated group after acute digitalization, even though the changes in pressure in the left ventricle and pulmonary artery were not impressive, there was a definite elevation of the left ventricular peak dp/dt. The latter finding confirmed the observations made by Mason and

Braunwald[23] that digitalis preparation is capable of stimulating the contractility of the nonfailing human heart.

The patients in the congestive group had an even greater response to acute digitalization manifested by augmentation of left ventricular peak dp/dt and stroke work. There was a striking decrease in left ventricular end-diastolic pressure, virtually to a normal level in each of the 3 patients studied. In addition a decrease in "central" and pulmonary blood volumes was observed in 2 patients (Cases 8 and 12). These changes indicate that the left ventricular dysfunction in these patients is at least temporarily reversible and that significant hemodynamic improvement can be achieved by the administration of digitalis preparations. Significant clinical improvement was also noted after acute and subsequent digitalization. However, it should be pointed out that the prognosis in these patients in general has been unfavorable, even though all were treated with a strict medical cardiac regimen. Three patients had died within 2 years after study and the other 3 patients are severely incapacitated at the time of this writing.

The hemodynamic changes in "restrictive" idiopathic cardiomyopathy have been described in many patients on the basis of the results of right heart catheterization.[7-9,13,15,18] The characteristic right ventricular diastolic dip-plateau which was demonstrated in all 3 cases in the present series has been attributed to a sudden early cessation of diastolic inflow resulting from a reduced limit of distensibility of the ventricle. In many cases this pattern has been indistinguishable from that seen in constrictive pericarditis or restrictive endocardial lesions.[19-22] Since, in restrictive cardiomyopathy, the process almost always involves both ventricles, an abnormal elevation of the diastolic pressures in both chambers is expected. However, because the systolic pressure in the right ventricle is normally only one fifth that in the left ventricle, a comparable rise in ventricular diastolic pressure produces a more striking dip-plateau pattern in the right ventricular pressure tracing than in the left. In the present series of 3 cases the left ventricular diastolic pressure was uniformly elevated. A left ventricular diastolic dip-plateau was also demonstrated in 2 patients.

In Case 15, cardiac catheterization was performed after the patient had improved considerably with treatment which included bed rest, a low-salt diet, digitalis and diuretics. On admission his venous pressure was approximately 30 cm. of H_2O and he was markedly orthopneic. If cardiac catheterization had been performed immediately after admission, it is certain that both the right atrial and right ventricular diastolic pressures would have been much higher.

The response to acute digitalization in 2 patients (Cases 13 and 14) of the restrictive group differed from that observed in 3 patients in the congestive group. In these 2 patients, only a minimal increase or no change in the cardiac index and stroke index occurred. No significant change was observed in the left ventricular, left atrial or pulmonary arterial pressures. In 1 patient (Case 14) there was a slight increase in both the "central" and pulmonary blood volumes, associated with a slight rise in the pulmonary arterial mean pressure. In both patients, however, moderate augmentation of the left ventricular peak dp/dt and stroke work was observed. No clinical improvement was observed in either of these 2 patients after acute digitalization. It should be emphasized again that it is very likely that 1 or 2 patients of the restrictive group probably had concurrent left and right ventricular decompensation as well.

The findings with respect to "central" and pulmonary blood volumes in all three groups of patients and the values estimated after acute digitalization deserve special comment. Duplicate determinations of "central" and pulmonary blood volumes in 42 patients studied in our laboratory revealed a standard deviation of a difference $\pm$ 41 ml./M.² in the former and $\pm$ 29 ml./M.² in the latter.[30] In a group of 10 patients with normal hemodynamics the values for "central" blood volume averaged 594 $\pm$ 63 ml./M.² (mean $\pm$ S.D.) and those for pulmonary blood volume 281 $\pm$ 25 ml./M.² (mean $\pm$ S.D.).[30]

In the compensated group, with the exception of Cases 1 and 5, both the cen-

tral and pulmonary blood volumes were within normal limits. In Cases 1 and 5 the central blood volume was probably increased. Surprisingly, in the congestive group the central blood volume was within normal limits in 2 of 4 patients, and the pulmonary blood volume was normal in 2 of 3 patients in whom it was measured. The values for central and pulmonary blood volumes were normal or below normal in all 3 patients in the restrictive group.

Of particular interest was the observation that after acute digitalization the values for central and pulmonary blood volumes generally fell in the compensated and congestive groups, particularly when there was a concomitant fall in the left ventricular end-diastolic pressure. On the other hand, acute digitalization in the restrictive group did not significantly decrease central blood volume, pulmonary blood volume, or left ventricular end-diastolic pressure. It would appear, therefore, that a close relationship existed between the measurements of volume and the response of the left ventricle to digitalization.

If the indicator-dilution technique adequately measures the central and pulmonary blood volumes in the patients under discussion, one must conclude that they are not uniformly elevated in the presence of postcapillary pulmonary congestion. The values measured must be the resultant of several opposing factors. For example, an elevated pulmonary venous pressure secondary to an increase in left ventricular diastolic and left atrial pressures would tend to increase the central and pulmonary blood volumes. On the other hand, persistence of these abnormalities may lead to redistribution of blood flow, permanent structural changes with probable narrowing of both pulmonary arteries and veins, and decreased pulmonary vascular compliance. These factors would then tend to limit or perhaps reverse the augmented central and pulmonary blood volumes. The duration of these "distending" influences and the homeostatic or pathologic alterations would seem to be important parameters in assessing the resultant volume values.

The concept of normal pulmonary blood volumes in the presence of postcapillary pulmonary congestion is at variance with traditional clinical impressions that "pulmonary congestion" is associated with an increase in pulmonary vascular volume as well as pressure. The data presented here would suggest that the pulmonary circulatory dynamics in the congestive group are at a point on the pressure-volume curve at which small increments in volume may produce large increases in pressure.

Summary and conclusions

1. The hemodynamic features of idiopathic cardiomyopathy have been presented in three categories: (a) a compensated group with normal hemodynamics, (b) a congestive group, and (c) a restrictive group. In none of these patients was left ventricular outflow obstruction demonstrated during infusion of isoproterenol, acute digitalization, or exercise. Systemic arterial pulse pressure of the postectopic beat was always greater than that of the control beat.

2. In the compensated group there was left ventricular hypertrophy evidenced by physical, electrocardiographic, and radiologic examination, but the hemodynamic findings were within normal limits.

3. The patients of the congestive group had compromised left ventricular function manifested by either markedly elevated left ventricular end-diastolic pressure or left atrial pressure, or both. The cardiac index, stroke index, and left ventricular stroke work were all significantly reduced. Most of these patients had pulmonary hypertension, but the right ventricular end-diastolic and right atrial pressures were normal in all but 1 patient.

4. The hemodynamic findings in the patients of the restrictive group were characterized by a dip-plateau pattern of the elevated right ventricular diastolic pressure associated with a significant elevation of the left ventricular end-diastolic pressure. In general, there was a little difference between the left and right atrial mean pressures. The symptomatology of the patients varied from slight exertional dyspnea to marked disability, depending upon the degree of impairment of ventricular function.

5. One important feature of the cases

presented is the finding of normal or only slightly increased central and pulmonary blood volumes, despite obvious post capillary pulmonary hypertension in the congestive and restrictive groups. It would appear that in these patients the blood volume in the pulmonary circulation and in the left heart depends upon the interaction of several factors. These probably include the height of left atrial pressure the extent of pulmonary vascular compliance, the degree of structural changes in the pulmonary vessel and the magnitude of left and right ventricular functional impairment.

6 The effect of acute digitalization in these three groups of patients is manifested by a uniform increase in the rate of rise in the left ventricular pressure pulse and an augmentation of the left ventricular work. In the congestive group a fall in the left ventricular diastolic left atrial and pulmonary arterial pressures was observed and this was usually accompanied by a decrease in both central and pulmonary blood volumes. In contrast no significant change was noted in either the pressures or the blood volumes in the left heart and pulmonary vascular bed of the patients with restrictive cardiomyopathy Thus, the response to acute digitalization may be helpful in differentiating the congestive group from the restrictive group.

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Experimental and laboratory reports

Cardiopulmonary effects of distention of the urinary bladder

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The chance observation of a patient in whom cardiopulmonary symptoms became worse coincidentally with distention of the bladder due to urinary obstruction and improved after catheterization led us to a study of the effects of distention of the bladder on cardiopulmonary function in dogs. A principal portion of these experiments deals with the possibility of bladder-associated alterations in the lung volume pressure relationship since such changes could explain the clinical observations. Thus volume-pressure relationship is an approximation of total thoracic static compliance.

Methods

All experiments consisted of control studies in anesthetized animals with emptied bladders, followed by studies in the same animals while their bladders were distended. Previous work suggests that the effect of anesthesia and trauma would not change significantly during the period of the experiment.

Twenty-one male dogs weighing between 12 and 24 kilograms were anesthetized with 27 mg. of intravenous pentobarbital per kilogram of body weight. In an additional dog (No. 3) intravenous Dial with urethane, 0.5 ml. per kilogram of body weight, was used as anesthetic. Tracheotomies were performed and the tracheotomy tubes were connected to a Palmer respirator pump, adjustable for rate and tidal volume.

For total thoracic volume-pressure relationships in 17 dogs the airway was switched from the Palmer pump at end expiration to a closed three-way circuit with a water manometer and a specially constructed device for injecting measured quantities of air. Measured volumes of air were quickly forced into the lungs serially and the pressure exerted against the manometer at each volume was recorded. At least five injections up to a total injected volume of 500 to 800 c.c. were used for each volume-pressure curve. A slight rise in pressure was occasionally observed when the dog's airway was switched from the Palmer pump to the volume-pressure circuit (see Fig. 1). This probably represents a small and inadvertent injection of air which produces a negligible shift of the true volume zero

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point below the graph. In each case the injected volume was measured at atmospheric pressure; hence it does not represent the absolute change in lung volume.

In 5 other dogs (Nos. 11, 13, 14, 15, and 16) the presence or absence of changes in compliance was inferred from the recording of pulmonary arterial pressure. When an individual breathes in and out, there are concomitant changes in intrathoracic pressure which usually cause slight alterations of the pulmonary arterial pressure during the respiratory cycle. If compliance decreases, the changes in intrathoracic pressure will be accentuated at any given volume and the effects on the pulmonary arterial pressure will be more noticeable. Therefore, if during a control study a dog showed little or no respiratory effect on the pulmonary arterial pressure but with a distended bladder had noticeably increased respiratory excursions of the pressure, a reduction in compliance was assumed. In these experiments, compliance was estimated by dividing tidal volume, in milliliters, by respiratory fluctuations in pulmonary arterial pressure, in millimeters of H_2O. This is inaccurate to the extent of respiratory variations in vascular resistance and stroke volume.[2] Unless the variation was greater than could be accounted for by these factors, no conclusions could be drawn. From our own experience with variations in stroke volume, we concluded that a change of 35 per cent would be greater than hemodynamic or measurement error factors could produce and implied changes in compliance, but not in a quantitative manner.

For determination of cardiac output and aortic pressure, femoral artery and vein cutdowns were performed, and polyethylene catheters were inserted through these vessels into the inferior vena cava and aorta, respectively. To get pulmonary arterial pressures, a cutdown was done on the right external jugular vein, and a radiopaque polyethylene catheter was inserted through the vein and the right side of the heart into the artery under fluoroscopic visualization.

Cardiac outputs were estimated by the method of Kinsman and associates,[3] using Cardio-Green, a tricarbocyanine dye, as an indicator, and inscribing a dye-dilution curve by means of a cuvette densitometer.*[3,4] For arterial pressures, variable inductance transducers were connected to a blood pressure control unit† monitored by an oscilloscope. Pressures and cardiac outputs were recorded on a Hathaway multichannel recorder‡ with an optical galvanometer system and photographic paper film.

Before the control determinations were begun, a polyethylene catheter was inserted through the urethral orifice into the bladder. The bladder was emptied and the catheter was connected via a three-way stopcock to a water manometer for pressure readings. After the control studies had been completed, measured volumes of saline were slowly injected into the catheter, and the pressures were recorded.

In some animals, postexperiment compliance studies were made about 10 minutes after deflation of the bladder; in others, autopsies were performed while the bladder was still distended, in order to ensure that the inflation procedure had been properly carried out.

In dogs, as in human beings, pressure in the bladder rises only slightly until a certain volume of intraluminal fluid accumulates. At this point the detrusor muscle contracts and there is a sudden sharp rise in pressure.[5] A pressure of 100 mm. of water was arbitrarily selected as indicative of distention of the bladder, and when this pressure had been attained the catheter was clamped; it was reopened at the end of the experiment, at which time the pressure was checked to be sure a satisfactory level had been maintained. Between 75 and 250 c.c. of injected saline were required for this degree of rise in pressure. Cardiopulmonary studies during distention of the bladder were made at least 15 minutes after a satisfactory bladder pressure had been established.

Results

Compliance. Direct measurements of the volume-pressure relationships were made in 17 dogs (see Table I,A). Twelve showed decreased compliance during distention

*Manufactured by Gilford Instrument Laboratories.
†Hathaway Type-MBC-2.
‡Type S-14-C.

Table I Total compliance at maximum intrathoracic pressure (volume in ml / pressure in mm H_2O)

Dog number	*Control*	*Experimental*	*Per cent change*
A. Direct compliance measurements			
3	7 10	5 10	−28 6
4	8 00	6 20	−22 5
5	9 40	4 90	−48 0
6	3 15	3 10	− 1 6
7	3 91	3 91	0 0
9	2 50	2 10	−16 0
10	2 70	2 65	− 1 8
17	3 45	2 72	−19 7
18	3 52	3 57	+ 1 4
19	3 45	2 50	−27 5
20	3 23	2 85	−11 8
21	3 45	3 09	−10 4
22†	8 45	7 45	−11 8
23	7 90	5 55	−29 9
24	7 70	4 75	−38 4
25	6 95	5 60	−19 5
26‡	6 00	5 70	− 5 0
B I ferred compliance measurement (*see text*)			
11	5 10	1 30	−75 0
13	3 40	3 40	00 0
14	0 45	0 50	+11 0
15	1 10	0 16	−85 0
16	0 47	0 22	−53 0

*The compliance differences in Group A are highly significant, t15 = 3 72, $p < 0.005$ Because of inherent inaccuracies in the data of Group B, statistical analysis was not done.

†T overcome struggling it was necessary to use dose of 32 mg per kilogram of Nembutal in this dog This may have altered the normal" response to inflation of the bladder

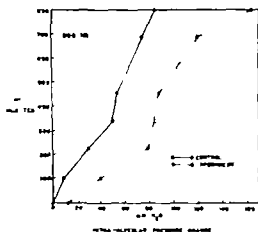
‡This experiment was carried out exactly as the others, except that distention of the bladder was not maintained. I served as control of the method and is not included in the statistical analysis of the data

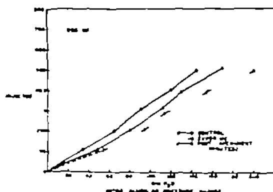
of the bladder as compared with the control value In 4 others there was no significant change while the bladder was inflated A mock experiment in one animal (No 26) resulted in no significant change

Compliance was estimated in 5 other dogs by using the pulmonary arterial pressure and tidal volume (see Table I,*B*) Three of the 5 dogs showed a decrease in compliance during distention of the bladder Thus, of the 22 dogs studied 15 had decreased compliance while the bladder was inflated and 7 demonstrated no significant change although one of the 7 did not have distention of the bladder and was not expected to have a change in compliance

Compliance curves after release of bladder pressure tended to lie between the experimental and control curves (see Fig 2) although in some instances they equaled or surpassed the control curves. Nearly all of the experimental curves showed a gradual decline in compliance with greater inflation of the lungs (Figs 1 and 2) indicating that the volume pressure relationship being measured and called "compliance was more complicated than a simple balloon inflation in which compliance increases as volume increases. An elastic limit effect might have been created by the shape of the animal operating board or the supine position of the dog

On the basis of these results the 13 dogs in which hemodynamic studies were made (Nos 3 6 7 11 13 14 15 16 22 23 24 25 and 6) were divided into two groups (roup I in which compliance decreased at high vesical pressures and Group II in which no difference in compliance was


Fig 1 Representative compliance curves


Fig 2 Compliance curve showing incomplete recovery

noted Studies of hemodynamic function revealed a separate pattern of changes in each group

Pulmonary arterial pressure In Group I 6 of the 7 dogs in which pulmonary arterial pressures were obtained had rises in both systolic and diastolic values during distention of the bladder as opposed to the control level (see Table II)

In one dog (No 11 see Fig 3) the pulmonary arterial pressure increased while the bladder was distended decreased slightly while the bladder was being emptied and returned to the control level within 5 minutes after bladder pressure returned to zero After deflation the pulmonary arterial pressure respiratory excursion which had appeared at the high vesical pressure was no longer present In another animal (No 15) however both increased pressure and decreased compliance were still present 10 minutes after relief of distention of the bladder

Attempts were made to determine the pulmonary arterial pressure in 3 dogs of Group II In one failure to inscribe a base line obscured the results. In another the catheter in the pulmonary artery slipped back into the right ventricle during the experimental run Although these technical difficulties prohibited quantitative accuracy in determining pulmonary arterial pressures the recordings in each *case showed no significant relative change* between control and experimental pressures. The third dog did not have an inflated urinary bladder when the observation on pressure was made.

Aortic pressure In Group I all 3 dogs in which aortic pressure was measured showed increases in both systolic and diastolic levels during distention of the bladder (see Table II) In Group II aortic pressures were recorded in 4 dogs. In 2 the pressure was unchanged and in 2 it decreased during distention of the bladder

Nothing was observed at the time of the experiment to explain the low control pressure in Dog No 15 Two of the 3 dogs of Group I (Dogs No. 15 and 16) displayed increased respiratory effect on the aortic pressure during distention of the bladder similar to that seen in the pulmonary arterial pressure.

Heart rate Six of 8 dogs in Group I had an increased heart rate during distention of the bladder The rate increased in 2 of 4 dogs in Group II (Dog No. 26 is not included because distention of the bladder was not present) In Dog No. 3 Dial with urethane was used for anesthesia whereas all other dogs were anesthetized with pentobarbital which may explain the slower heart rate in the former animal

Cardiac output Five of 6 dogs studied in Group I had increased cardiac outputs during distention of the bladder whereas circulation time decreased (when it was measured) and central blood volume increased in 3 (see Table III) Cardiac output decreased in both of the dogs of Group II in which it was measured (Dog No 26 is again excluded since it did not have distention of the bladder)

Table II *Pressure and heart rate data*

Dog number	Pulmonary arterial pressure (mm Hg)			Aortic pressure (mm Hg)			Heart rate (per min)		
	Control	Experimental	Δ	Control	Experimental	Δ	Control	Experimental	Δ
Group I Compliance decreased									
3	—	—	—	180/95	195/110	+15/15	86	100	+14
11	13/3	38/23	+25/20	—	—	—	210	212	+ 2
15	22/18	31/24	+ 9/6	75/55	133/105	+58/50	171	228	+57
16	28/14	36/20	+ 8/6	122/87	150/126	+28/39	190	199	+ 9
22†	7/2	8/3	+ 1/1	—	—	—	150	180	+30
23	5/4	7/5	+ 2/1	—	—	—	180	180	00
24	11/6	9/4	− 2/2	—	—	—	160	160	00
25	19/10	23/13	+ 4/3	—	—	—	90	120	+30
Group II No change or increase in compliance									
6	—	—	—	120/95	115/95	− 5/0	210	220	+10
7	—	—	—	122/95	122/100	+ 0/5	164	164	00
13		(Qualitatively no)		137/108	113/78	−24/30	185	185	00
14		(Change—see text)		195/140	140/105	−55/35	133	206	+73
26‡	9/3	6/3	− 3/0	—	—	—	180	180	00

Δ = Experimental Control data.
†See footnote to Table I.
‡See footnote to Table I.

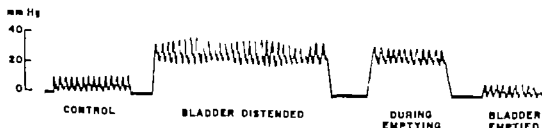


Fig 3 The effect of distention of the bladder on pulmonary arterial pressure.

Discussion

The concept that distention of the urinary bladder could induce cardiopulmonary effects was first advanced by Talaat,[6] in 1937 and supported by Watkins[7] in 1938 who observed that distention of the bladder with saline resulted in increased blood pressure in anesthetized animals. Guttman and Whitteridge[8] reported that during cystometrographic examinations, patients with high transections of the spinal cord were subject at high vesical pressures to circulatory changes which varied with the site of the injury. Agrest and Roncoroni studied 2 patients with paraplegia secondary to traumatic damage of the spinal cord and found that distention of the bladder caused both pulmonary and femoral arterial pressures to rise without affecting cardiac output or central blood volume.

However Berman and Rose[1] studied intact anesthetized dogs and failed to find significant cardiovascular alterations in response to inflation of the bladder.

Our studies indicate that distention of the urinary bladder has cardiopulmonary effects in anesthetized dogs. Although not

Table III Flow and volume data

Dog number	Cardiac output (L./min.)			Circulation time (sec.)			Central blood volume (ml.)		
	Control	Experimental	% Δ	Control	Experimental	% Δ	Control	Experimental	% Δ
Group I Compliance decreased									
3	1 08	1 32	+22	11 3	9 0	−20	203	198	− 2
16	2 28	2 50	+10	5 4	4 8	−11	205	200	− 2
22†	2 85	2 55	−10	—	—	—	285	280	− 2
23	1 46	1 80	+23	—	—	—	173	186	+ 7
24	6 23	7 35	+18	—	—	—	579	646	+12
25	0 98	1 84	+88	—	—	—	215	266	+24
Group II No change in compliance									
6	2 60	2 00	−23	7 9	7 9	00	342	263	−23
7	3 72	2 80	−25	6 7	6 4	− 4	415	392	− 6
26‡	2 10	2 00	− 5	—	—	—	333	333	0

*% Δ = Experimental-Control/Control × 100
†See footnote to Table I
‡See footnote to Table I

all dogs tested demonstrated identical changes there is a striking and convincing similarity in the changes seen in the dogs of Group I The cardiopulmonary changes in Group I probably represent a characteristic physiologic response to distention of the bladder and for some unknown reason such as individual variability inadvertent differences in technique, or inadequate sensitivity of measuring devices the minority in Group II failed to show the characteristic response

Quite likely the observed effects of distention of the bladder are part of a reflex. Receptors in the bladder may respond to changes in pressure and by a neural or humoral mechanism cause cardiopulmonary changes The negative results of Berman and Rose[1] may have been due to their bladder inflation technique by which saline was injected very rapidly and at such high pressure that in some dogs the bladder burst. Possibly bladder receptors were unable to respond to the infusion either because of the speed of the injection or because of the extreme and unphysiologic pressure under which it was done

The compliance estimated in these experiments is that of both lung and thoracic wall Since there are concurrent related hemodynamic changes it is most likely that the primary cause of the reduction in compliance is in the lung alone although without additional data increased tone of the thoracic musculature cannot be ruled out as a possible influence Either would increase the work cost of breathing

A probable cause of the reduced compliance is change in the elastic properties of the lung although decreased lung volume or mid position are possible causes, since they would tend to shift the volume-pressure curve. Increased intra abdominal pressure from the distended bladder is unlikely in view of the small size of the organ Bronchoconstriction which is commonly associated with reduced total compliance may have been a factor in these experiments. While the bladder was inflated expirations appeared to be prolonged in most dogs of Group I suggesting that increased airway resistance was present The slight rise in central blood volume in some animals may have contributed to the impairment in compliance Whatever the reason more pressure is required to move a given volume of air after distention of the bladder

The increased cardiac output is accounted for largely by increased heart rate but there is also a small increase in stroke volume It is possible that the

sympathetic nervous system may be involved in these phenomena, since both increased heart rate and increased strength of cardiac contraction are well known effects of sympathetic stimulation

Since cardiac output is increased it must be involved in the rises in pulmonary arterial and aortic pressure. Unfortunately simultaneous determinations of cardiac output and arterial pressures were not obtained and it is impossible, therefore, to calculate pulmonary or systemic vascular resistances. However the studies of Agrest and Roncoroni[9] suggest that both pulmonary and systemic resistances rise with distention of the bladder in paraplegic patients.

The possibility that distention of the bladder may result in cardiopulmonary embarrassment of sufficient severity to cause dyspnea is of practical clinical importance Sudden onset of unexplained dyspnea in a patient with a cardiorespiratory disorder should be an indication for study of the urinary tract. Careful attention should be paid to the maintenance of patency of the urinary tract not only for reasons related to the tract itself but also because distention of the bladder may exacerbate cardiovascular or pulmonary symptoms. Indeed it seems to be likely that distention of the bladder in an extremely ill patient could be a lethal complication by virtue of the cardiopulmonary effects.

Summary

Cardiopulmonary function was studied in 22 anesthetized dogs before and during distention of the urinary bladder Fifteen of the 22 demonstrated a reduction in total thoracic compliance during distention The group of dogs with decreased compliance also showed increased aortic and pulmonary arterial pressures, increased cardiac output inconstantly increased central blood volume, and increased heart rate. It is concluded that these results establish an effect of distention of the bladder on cardiopulmonary function and it is suggested that a neural or humoral reflex mechanism is in operation. These changes are of potential clinical significance.

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Muscle fiber content of the heart in African cardiomyopathy

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The morphologic features of the hearts of patients dying from African cardiomyopathy were first described by Higginson and associates.[1] Their description requires little modification. The major change is a fibrosis. The actual weight of abnormal fibrous tissue is quite patently unable to account for more than a negligible fraction of the increase in heart weight. In immediate association with areas of fibrosis, hypertrophy of muscle fibers is evident microscopically but the areas are so limited in extent in relation to the whole bulk of muscle tissue that in the past general hypertrophy has been presumed. No studies have yet been carried out to quantitate changes in muscle fibers. Such a study is reported here.

Methods

Hearts were obtained at postmortem from patients in whom the clinical and pathologic diagnoses were considered to be secure and uncomplicated by pulmonary hypertensive rheumatic coronary or other cardiac disorder. They were compared with the hearts of patients matched as to sex, age (within 3 years) and weight (within 15 pounds) who died soon after severe trauma. There were 19 in each group, of whom 14 were males. The hearts were weighed free from blood. The thickness of the wall at standard sites was measured in situ to within 1 mm. Blocks were taken to include the measured edges and were fixed for 5 days in formol-saline embedded and sectioned at 5 μ then mounted and stained according to standardized procedure. The sections studied were those taken as close as possible to the measured cut edge of the block of muscle. The two standard sites were in the right ventricle 1 to 2 cm below the pulmonary valve and 1 cm to the right of the interventricular septum anteriorly and in the left ventricle 2 to 3 cm below the mitral ring directly behind the free upper end of the inferior papillary muscle (see Fig 1). The cut making the free edge was directed to the apex of the heart and the points defined above were the upper limit of the block.

The hearts were then deepfrozen and later thawed for cutting and separate weighing of ventricles and septum according to the method of Fulton and associates,[2] except that no formalin fixation was used. Correction was made for minor dehydration shown by loss of weight during freezing and the weight of tissue blocks removed was ignored being of the order of 2 grams.

The stained sections were projected onto the screen of a Zeiss Visopan. Three

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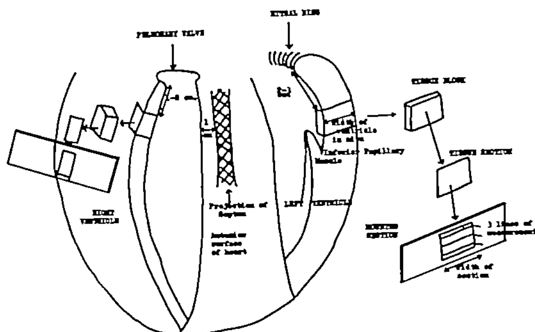


Fig. 1. Diagrammatic illustration of the method of obtaining and measuring sections.

different measurements were made (1) the whole width of the section as shown in the figure, (2) the number of muscle fibers, and (3) the total thickness of muscle fibers. Each of these measurements was made in the same direct transverse line from epicardium to endocardium. The measurements were made in three such lines in each section (see Fig. 1) and averages from these three lines are the basis for the figures in Table I. A selection of the exact lines along which to measure had to be made. The criteria were that they should be from points at which no trabeculae carneae elevated the endocardial surface, that from inspection of the section they should look representative, and that they should be widely spaced from one another.

Results and discussion

The main results are given in Table I. The measurements on the Visopan are given uncorrected since correction for magnification brings the result back only to the width of the section, not to the width of the original fresh muscle. The table shows two main points. Significant differences between normal and abnormal emerge only in the comparisons of heart weight, and in the right ventricular measurements of wall thickness and width of the muscle fiber element, the differences there being relatively minor. There is conspicuous absence of differences in left ventricular measurements, whether of total wall thickness, total muscle fiber thickness, or muscle fiber number and absence also of differences in right ventricular muscle fiber number.

It is difficult to assess how much the right ventricular hypertrophy contributed to the increase in the weight of the whole heart. From normal to abnormal the mean weight of the free right ventricular wall was increased by 54 to 100 grams, and of the septum plus free left ventricular wall (taken together following Fulton and associates[1]) by 163 to 288 grams. Total gain in cardiac weight was 249 grams, so that the right ventricle contributed only 22 per cent of total gain. Since total right ventricular muscle fiber diameter was increased relatively slightly from 527 to 631 mm on the Visopan muscle fiber hypertrophy would seem to have formed only a minor part of this already small right ventricular contribution.

The right ventricular increase from normal to abnormal was 117 per cent

Table I. Measurements of heart weight and number and thickness of muscle fibers in patients with cardiomyopathy and in normal control subjects

		CCF	Normal	p
Male				
Weight of heart (grams)		568 ± 117	294 ± 44	< .001
Width of ventricle (mm.) by ruler at postmortem	R	5.0 ± 2.2	3.8 ± 1.0	< .1
	L	13.0 ± 3.3	13.6 ± 2.6	
Width of ventricle as seen on Visopan (mm.)	R	1 466 ± 263	1 306 ± 288	
	L	4 412 ± 251	4 259 ± 346	
Total width of muscle fibers as seen on Visopan (mm.)	R	619 ± 168	526 ± 29	= .05
	L	2 062 ± 276	2 134 ± 138	
Number of muscle fibers	R	133 ± 33	111 ± 27	
	L	260 ± 70	256 ± 79	
Female				
Weight of heart (grams)		433 ± 63	258 ± 37	< .001
Width of ventricle (mm.) by ruler at postmortem	R	5.0 ± 1.6	4.25 ± 0.66	
	L	14.75 ± 1.7	13.4 ± 1.6	
Width of ventricle as seen on Visopan (mm.)	R	1 689 ± 538	1 150 ± 66	< .1
	L	3 936 ± 1 183	4 257 ± 316	
Total width of muscle fibers as seen on Visopan (mm.)	R	665 ± 21	531 ± 20	< .001
	L	2 100 ± 424	2 171 ± 139	
Number of muscle fibers	R	109 ± 33	118 ± 18	
	L	261 ± 44	235 ± 69	
Both sexes				
Weight of heart (grams)		533 ± 120	284 ± 46	< .001
Width of ventricle (mm.) by ruler at postmortem	R	5.0 ± 1.5	3.9 ± 1.0	< .02
	L	13.5 ± 3.0	13.5 ± 2.5	
Width of ventricle as seen on Visopan (mm.)	R	1 525 ± 352	1 265 ± 256	< .02
	L	4 287 ± 638	4 259 ± 332	
Total width of muscle fibers as seen on Visopan (mm.)	R	631 ± 174	527 ± 30	< .05
	L	2 072 ± 292	2 144 ± 133	
Number of muscle fibers	R	112 ± 30	113 ± 24	
	L	260 ± 63	251 ± 75	

The p values from t test are given whenever they are below .1. Values are means ± standard deviation. Visopan measurements are uncorrected (see text). Figures are for 14 males and 5 females. CCF: Cardiomyopathy cases.

septal plus left ventricular increase was 130 per cent. The proportionate increase was therefore, much the same for the two chambers.

Scarring in this disease affects particularly the ventricles at the apex, and the bulk of muscle, particularly away from the apex, can look virtually normal. Changes in the sites sampled are to the eye representative of changes in these nonscarred parts of the ventricle, and it can be inferred that a major cause accounting for change in weight must be an increase in the length of fibers of the ventricles without change in their number. The increase in right ventricular muscle width could well be secondary to the left ventricular failure. If then the cause of the heart failure lies within the heart itself it is a failure of contraction unaccompanied by significant loss of muscle fibers, or change in their transverse size over the bulk of the ventricles.

Summary

Measurements were made, on microscopic sections of muscle fiber size and number in 19 cases of African cardiomyopathy. These measurements were made at standard left and right ventricular sites away from the apical areas of scarring. The only significant differences from normal controls were a greater total muscle fiber width in the right ventricle and total wall width. Total heart weight and right ventricular wall thickness as measured in situ at postmortem were also significantly greater.

It is inferred that the great increase in weight of the hearts is largely due to elongation of muscle fibers and that failure of contraction is not due to numerical loss of muscle fibers over the bulk of the ventricle.

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The anatomy and blood supply of the papillary muscles of the left ventricle

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The recent delineation of the clinical picture[1] and the electrocardiographic changes[2] seen with papillary muscle infarction have aroused interest in the structure, function, and blood supply of these regions.

Over the past 2 years we have carried out postmortem angiographic studies on human hearts, making detailed observations on the blood supply to the left ventricular free wall and the associated papillary muscles. The following report is based on these observations.

Methods and case materials

The 58 cases included in this study were selected from routine autopsies. Because of the interests of the authors, a higher percentage of the cases chosen had some form of heart disease, but the series also included cases with no known cardiovascular disease, as listed in Table I. The age of patients ranged from 2 months to 80 years.

At autopsy the heart was removed and cannulae were tied in the right and left coronary orifices. The coronary vascular bed was flushed with isotonic saline for a period of 10 minutes, after which the

Table I. Clinical diagnoses in 58 cases

No heart disease	21
Coronary artery disease	20
Hypertensive cardiovascular disease	6
Hypertensive cardiovascular disease plus coronary artery disease	4
Congenital heart disease	3
Rheumatic heart disease	2
Myocarditis	2

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vessels were perfused with an injection mass similar to that described by Schlesinger[1] except that the barium sulfate was of a very small particulate size (Micropaque). The injection was carried out at room temperature at an arbitrary pressure of 100 millimeters of mercury for 20 minutes, after which the heart was cooled to hasten solidification of the injection mass. Stereoscopic anteroposterior and lateral radiographs were then made at a 40-inch tube-film distance. These films were inspected and served as a guide for the subsequent examination of the coronary vessels and myocardium which was carried out after a 24-hour period of fixation of the heart in 10 per cent formalin.

After these examinations several regions of myocardium were removed for more detailed radiologic and histologic studies. These included sections of the left ventricular free wall and the papillary muscles. The sections of free wall were longitudinal sections from base to apex, from 1 to 2 cm in thickness. Such sections were usually taken from both the anterolateral and posteromedial papillary muscle. These areas were studied radiologically using a beryllium window industrial type unit, and a technique similar to that described by Hale



Fig. 1. Papillary muscle which is tightly bound to the ventricular wall by extensions of the trabeculae carneae. Most of the trabecular bridges contain vascular channels.



Fig. 2. Papillary muscle which is attached to the ventricular wall by muscular trabecular bridges and by fine thread-like bridges. The thin bridges may also contain vascular channels.

and Reed for brain slices The ventricular wall sections were placed directly on a light tight packet of Eastman type M film and exposed at 20 to 25 kilovolts and 6 milliamperes for a period of 2 minutes. The tube film distance was 12 inches Some exposures were made using the underwater technique described by Fulton [4]

General anatomic considerations

The papillary muscles are a specialized form of the trabeculae carneae and often resemble an exaggerated portion of the trabeculae with a free extremity to which are attached the chordae tendineae The many folds of the trabeculae plus other thread like bands continue over to the papillary muscle holding it firmly to the left ventricular wall even to its tip as seen in Figs 1 and 2 Very seldom does one see a left ventricular papillary muscle which is truly free from the adjacent ventricular wall

In the left ventricle there are usually two groups of papillary muscles One group (the posteromedial) lies posteriorly near the attachment of the posterior free wall of the left ventricle to the interventricular septum The other group (the anterolateral) lies on the anterolateral free wall These usually consist of a set of two or even three well-defined but closely associated structures each with chordae tendineae attached at the tip



Fig 4 An example of dilatation of the left ventricular chamber due to idiopathic myocarditis. Note that the apical segment of the chamber is dilated and elongated causing an apparent migration of the papillary muscle toward the base. The longitudinal axis of the muscle is no longer parallel to the longitudinal axis of the chamber



Fig 3 An example of concentric hypertrophy of the heart due to hypertensive vascular disease showing the proportionate thickening of the papillary muscles and the preservation of the usual arrangement of the longitudinal axis of the papillary muscle with respect to the left ventricular chamber

The axis of the papillary muscles is generally oriented in a direction parallel to the axis of the left ventricular cavity In concentric left ventricular hypertrophy the papillary muscles become proportionately thicker in diameter preserving the same axial direction as in the normal heart An example is seen in Fig 3 In dilatation of the left ventricular chamber the dilatation predominantly involves the apical region thus causing the papillary muscles to appear to move upward toward the valve ring as seen in Fig 4 This effect has also been noted by Grant [8] The axis of the papillary muscles in such cases is tangential to that of the ventricular chamber which may explain in part the mitral insufficiency often found in conjunction with left ventricular dilatation

The blood supply of the left ventricular papillary muscles has been well-docu



Fig. 5. Longitudinal section from the ventricular wall, showing the vascular supply to the anterolateral papillary muscle. The section is from the heart of a 52-year-old man with no cardiac abnormalities, who died of acute arsenic intoxication.

mented by Gross[7] and Spalteholz.[8] The anterolateral papillary muscle is usually supplied by marginal tributaries from the circumflex branch of the left coronary artery. The supply of blood to the posteromedial papillary muscle is more variable reflecting the variability of the supply of blood to the region of the posterior septal attachment. Spalteholz[8] observed that in hearts with a predominent left circulation the left coronary via the circumflex artery may supply the posterior papillary muscle. On the other hand in hearts with a predominant right circulation the muscle is supplied by posterior descending branches of the right coronary artery.

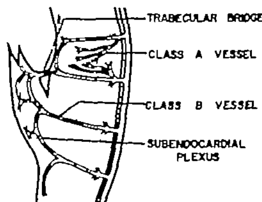


Fig. 6. Diagrammatic representation of the blood supply to the normal papillary muscle showing the segmental arrangement of Class B vessels and the subendocardial plexus.

Results

A. Ventricular wall. The intramural course of the blood vessels supplying the papillary muscles is of considerable interest. The larger epicardial branches of the coronary tree are seen to course in a radial direction from the atrioventricular groove toward the apex usually in the subepicardial fatty tissue but occasionally 1 or 2 mm. beneath the surface of the myocardium. The arborizations from these branches plunge at right angles to their parent vessels entering the myocardium and rapidly subdividing into a meshwork of fine vessels from 400 to 1,500 microns in diameter. The finer arborizations (Class A) divide quickly in the myocardium forming a series of very fine branches in the area of the middle and outer thirds of the myocardium. The larger arborizations (Class B) divide less frequently and maintain their diameter as they course inward. They terminate in an anastomotic network of large caliber[9] which is located in the subendocardial layers of the myocardium including the trabeculae carneae and the papillary muscles. Each papillary muscle is supplied by several of these large Class B channels which generally have a segmental distribution as seen in Fig. 5 and diagrammatically in Fig. 6. The base mid portion and tip receive separate tributaries each originating from epicardial vessels radially outward.

The complex trabeculations and bands between trabeculae carneae and the papillary muscles are often seen to carry these vessels into the papillary muscle. Once the nutrient vessels enter the papillary muscles, they enter the large inner anastomotic network, which is generally oriented in the direction of the papillary muscle and the nearby trabeculae carneae. Some arcades belonging to this subendocardial network are seen to run 1 to 2 cm. along the subendocardial surface parallel to the folds of the columnae carneae. Further observations on the subendocardial network are reported in another publication from this laboratory.[9] Occasional vascular channels of a size sufficient to be easily seen with the eye are observed to cross the cavity in very fine thread like extensions of the trabeculae carneae. In one case vascular connections were seen to enter the muscle from the region of the valve ring following the chordae tendineae.

The supply of blood to the papillary muscle is disturbed in several ways by disease of the coronary vessels. In areas of scattered fibrosis, there is an apparent overgrowth of small (Class A) vessels, which may extend into the papillary muscle. In such areas the Class B vessels may remain intact and the large vessels of the papillary muscle may appear to course through such areas without major distortion. In areas of heavy fibrosis or scar formation such as is seen in old myocardial infarction the vascular supply to the papillary muscle is altered more profoundly. In such cases, the regular radial arrangement

of Class B vessels in the ventricular wall is obliterated As a result there is no longer a segmental arrangement of the vessels of the papillary muscle In such cases, the papillary muscle may show extensive fibrosis but there are usually islands of intact muscle cells which appear to be supplied by extensions of the subendocardial plexus which course in a direction parallel to the endocardium instead of in a radial direction through the ventricular wall. An example is seen in Fig 7

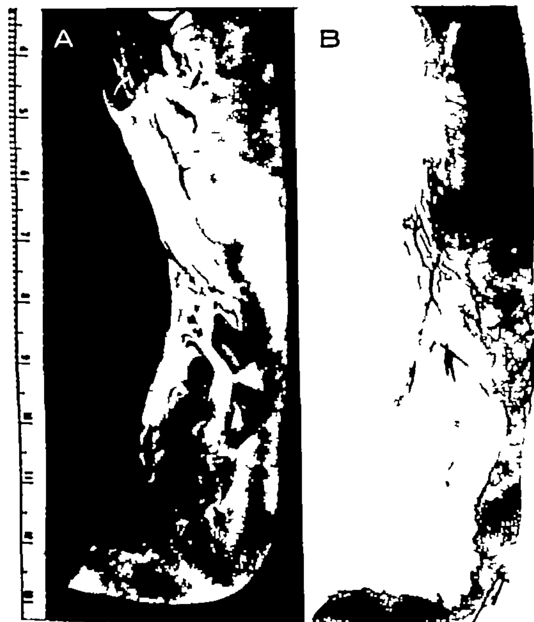


Fig 7 A A papillary muscle which has been extensively involved by old and new myocardial infarcts There is extreme thinning and scarring of the lower ventricular wall, but there is an intact area of trabecular muscle at the base of the papillary muscle. *B* A radiograph of the same area seen in *A* Note that the usual segmental arrangement is markedly altered. The intact trabecular muscle received its vascular supply through an extension of subendocardial vascular channels.

All six of the examples of extensively fibrotic papillary muscles seen in this series were associated with occlusive disease of the coronary vessels, but occasional examples of fibrosis of the tip of the papillary muscle were seen in the hearts of older individuals. In these cases this appeared to be an extension of the fibrosis usually seen in normal hearts at the point of attachment of the chordeae tendineae

In a previous report[9] we postulated that a reduction in the perfusion of the entire coronary bed such as might be seen in shock, in bilateral coronary ostial disease, etc might lead to inadequate perfusion of the subendocardial layers as a total unit, explaining the occasional occurrence of extensive subendocardial infarct Since the papillary muscles and the subendocardial layers share the same supply of blood and since the papillary muscles are the thickest subendocardial region it is thought that infarction and subsequent rupture may be produced on rare occasions by shock or by a lowered blood pressure in the face of generalized occlusive disease of the large coronary vessels

Summary

The supply of blood to the papillary muscles is segmental in distribution, and reaches the muscle from large penetrating branches originating from epicardial vessel located radially outward from the muscle The tip mid portion and base generally receive their vascular supply from separate tributaries which have a radial arrangement Fibrosis of the papillary muscles is most often associated with occlusive disease of the large coronary vessels. The vascular alteration accompanying this fibrosis is of two types (1) a fine overgrowth of Class A vessels, without interruption of the Class B vessels, and (2) an interruption of all channels, with enlargement of subendocardial vessels, suggesting the utilization of these vessels in the formation of collaterals past the occluded area

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An effect of quinidine sulfate on the lipid facilitated transport of calcium ions in cardiac muscle

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There is now abundant evidence to show that the extracellular concentration of ionized calcium influences the contractions of cardiac muscle[1-4] The actual accumulation of calcium ions by cardiac muscle cells under conditions of increasing contractility has been demonstrated using radioactively labeled calcium[5-8] Such a cellular accumulation of ionized calcium reflects the ability of these ions to traverse cell membranes and hence, to be transported from an aqueous to a lipoidal phase.[9]

Tissue lipids extracted from the cell membranes of skeletal muscles and nerves have recently been shown to facilitate the transport of calcium ions from a methanol aqueous phase to chloroform. The presently available data[10] indicate that local anesthetics, including procaine hydrochloride interact with the lipids extracted from skeletal muscle cell membranes and nerves in such a way that they inhibit this lipid facilitated transport of calcium It has been suggested that the reaction of such local anesthetics with the lipids of cell membranes may underlie the inhibitory effect of the local anesthetics on cellular ion fluxes, and that this may provide the basis for their anesthetic action[10]

The following experiments were performed to determine whether lipids extracted from cardiac muscle cell membranes resemble those similarly extracted from skeletal muscle cell membranes in their ability to facilitate the transport of calcium ions from an aqueous to a lipid solvent phase and if so, to determine whether quinidine sulfate inhibits this lipid facilitated transport of ionized calcium

Materials and methods

Rabbits were stunned by a blow on the head and the hearts were immediately excised and, while beating immersed in an ice-cold aqueous solution containing 0 1 M KCl + 0 005 M histidine, pH 7 4 Atria and superficially located deposits of fat were discarded the ventricles were then weighed and homogenized in ice-cold 0 1 M KCl + 0.005 M histidine. Homogenization was effected with a Potter Elvejehm type of homogenizer with a smooth glass tube and Teflon pestle operated at 1 425 r p.m The final volume of the homogenate was adjusted to provide a 10 per cent suspension (w/v referred

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to wet weight of tissue). This method of extraction is based on that described by Martonosi and Feretos.[11]

Preparation of membrane microsomal lipid fraction. The homogenate was centrifuged at 600 × g for 15 minutes at 2°C in a Servall refrigerated centrifuge to remove nuclei and cell debris. The sediment was discarded and the supernatant centrifuged at 10,000 × g for 30 minutes at 2°C to remove mitochondria. The mitochondrial pellet was discarded and the supernatant centrifuged at 104,000 × g for 60 minutes in the No. 30 head of a Spinco preparative ultracentrifuge. The resultant pale pink sediment consisting of membrane fragments and microsomes was resuspended in a volume of Ringer's solution equal to two thirds of the supernatant above the final microsomal membrane sediment. The Ringer's solution, prepared from Merck analytical reagent grade chemicals dissolved in all-glass distilled water, had the following composition in millimoles: NaCl 116, KCl 3.2, $CaCl_2$ 0.35. Freedom from mitochondrial contamination was confirmed by the absence of succinic dehydrogenase activity.[12] Aliquots of this membrane microsomal suspension were then extracted for 60 minutes with 1.5 ml. of chloroform-methanol solution (2:1) per milligram of microsomal membrane protein as described by Feinstein.[18] The chloroform-methanol extract was then separated by centrifugation at 900 × g for 30 minutes at 2°C. The protein concentration of the membrane microsomal fraction was determined as described by Lowry and associates,[19] using bovine albumin as the standard.

Effect of membrane microsomal lipid extract on calcium transport into the lipid solvent phase. The uptake of calcium into the lipid-solvent phase was measured by mixing 1.0 ml. of the chloroform-methanol lipid extract, which contained the lipid extracted from 1 mg. of membrane microsomal protein, with 1.0 ml. of Ringer's solution containing Ca^{45} in both the presence and absence of quinidine sulfate. The reaction mixture contained approximately 0.15 μc of Ca^{45} per milliliter. The reaction was performed in a separating funnel and after 15 minutes of vigorous mixing the two phases, one chloroform and the other water plus methanol, were separated. Aliquots of the chloroform phase were evaporated on stainless-steel planchets, and the radioactivity was determined using a gas flow counter.*

Results

Throughout these experiments considerable care was taken to ensure that the glassware remained free from radioactive contamination since Chujyo and Holland[14] and Niedergerke[15] have reported that glass surfaces absorb tracer calcium which subsequently may be released. To avoid such contamination the glassware used during the present experiments was acid washed and checked for contamination before reuse. Blank solutions containing 1 ml. of Ringer's solution and 1 ml. of 2:1 chloroform-methanol mixture were included in each series.

Table I shows the results obtained from five typical experiments. The incubation of Ringer's solution containing Ca^{45} with an equal volume of 2:1 chloroform-methanol solution did not result in the transport of Ca^{45} into the chloroform phase. The inclusion of lipids extracted from the cell membrane microsomal fraction as described above resulted in Ca^{45} being accumulated in the chloroform phase. Similar results were obtained from experiments in which the lipids were extracted from membrane-microsomal fractions isolated from toad (*Bufo marinus*) cardiac cell membranes. Under the conditions of the above experiments performed at 25°C, lipids extracted by the chloroform-methanol solution from 12 aqueous suspensions of rabbit cardiac cell membrane microsomal preparations containing 1 mg. per milliliter of protein effected the transport of 0.05 ± 0.006 μM of Ca^{++} from the aqueous to the lipid solvent (chloroform) phase.

In the presence of the extracted lipids the transport of Ca^{45} from Ringer's solution to chloroform was complete after 10 minutes of incubation. Lipids extracted from membrane microsomal preparations which had been stored at 0°C for 5 days were approximately 75 per cent more active in their ability to facilitate the transport of calcium ions than were the lipids which

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Table I Effect of rabbit heart membrane microsomal extract on transport of calcium into chloroform from an aqueous phase*

Preparation number	µM Ca^{++} in CHCl phase	
	Ringer + chloroform methanol	Ringer + chloroform methanol + extract
1	0 00	0 054
2	0 00	0 049
3	0 00	0 046
4	0 00	0 058
5	0 00	0 048

*Rabbit heart membrane-microsomal fraction extracted with 1.5 ml of chloroform methanol solution (2 1) per milligram of membrane-microsomal protein. The reaction mixture contained 1 ml of Ringer solution plus 1 ml. of chloroform methanol (2:1) solution with and without the lipid extract.

had been extracted from the freshly prepared membrane-microsomal preparation Throughout these experiments, fractions which had been stored at 0°C for more than 5 days were discarded

The addition of aqueous solutions of quinidine sulfate to the reaction mixture inhibited the lipid facilitated transport of calcium ions from Ringer's solution into chloroform The percentage inhibition varied according to the concentration of quinidine sulfate used The results of a typical experiment are displayed in Fig 1 in which it is shown that 100 µg per milliliter of quinidine sulfate inhibited by 85 per cent the ability of the extracted lipid to promote the transport of calcium ions into the chloroform phase.

The extent to which the transport of calcium ions was inhibited by quinidine sulfate varied from preparation to preparation but inhibition was invariably detected in the presence of 5 µg per milliliter of quinidine sulfate Typical results are listed in Table II

Discussion

The present results show that lipids extracted from cell membrane-microsomal fractions of rabbit ventricular muscle resemble those similarly extracted from skeletal muscle and nerves[1] in that they facilitate the transport of calcium ions from an aqueous to a lipid-solvent phase. In addition the above-mentioned results show that quinidine sulfate interacts with this lipid-calcium transport system in such

Table II Effect of quinidine sulfate on the lipid facilitated transport of calcium from an aqueous phase into chloroform*

Preparation number	µM Ca^{++} in CHCl phase					
	Solutions					
	Ringer + chloroform methanol	Ringer + chloroform methanol + extract	Ringer + chloroform methanol + extract + quinidine sulfate			
			5	25	50	100 µg/ml
6	0 00	0 056	—	—	0 011	
7	0 00	0 066	—	—	0 016	0 00
8	0 00	0 054	0 038	0 0 2	0 010	0 00?
9	0 00	0 045	0 036	—	0 018	
10	0 00	0 052	0 041	0 0 4	—	0 004
11	0 00	0 048	0 039	0 028	0 014	—

*Lipids extracted from rabbit heart membrane-microsomal fraction, using 1 5 ml chloroform methanol 2 1 per milligram of membrane-microsomal protein.

Reaction mixture contained 1 ml of chloroform methanol solution with and without lipid extract, [illegible] ml of Ringer solution containing Ca^{45} and quinidine sulfate as shown.

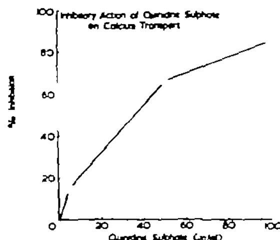


Fig. 1. The effect of quinidine sulfate on the lipid facilitated transport of calcium from an aqueous phase to chloroform. The reaction mixture contained 1 ml of chloroform-methanol (2:1) containing the lipids extracted from 1 mg of rabbit heart membrane-microsomal protein and 1 ml of Ca[45] labeled Ringer's solution, as indicated. Calcium transport was calculated from radioactivity appearing in the chloroform phase.

a way that the drug effectively impedes the transport of calcium ions from an aqueous to a lipid-solvent phase. The extent to which quinidine sulfate inhibited this transport of calcium varied according to the concentration of quinidine sulfate used but some inhibition was detected when 5 μg per milliliter of quinidine sulfate was used, *a concentration which is within the limits of concentration used clinically.*[6]

The effect of quinidine sulfate on the transport of calcium ions from the aqueous to the lipid-solvent phase (chloroform) appears to resemble that reported for the action of local anesthetics on the transport of calcium effected by lipids extracted from skeletal muscle cell membranes and nerves.[16] Feinstein recently reported that procaine hydrochloride interacted with the lipids extracted from rabbit skeletal muscle microsomal fractions in such a way that their ability to facilitate the transport of ionized calcium into the lipid-solvent phase was impaired. Ehrenpreis[17] extracted a phospholipoprotein from the electric organ of electric eels and found that this phospholipoprotein combines with calcium and with a number of neurogenic agents, including tetracaine and eserine. These and other observations substantiate Feinstein's conclusion that the divalent cations and the anesthetic drugs react with phosphate groups of phospholipoproteins lining the pores of cell membranes in such a way that the influx of sodium ions through these pores is impeded.

Many investigations, including those of Weidmann,[18] Johnson and Robertson,[19] and Klein and associates,[20] have already demonstrated that the action of quinidine on cardiac muscle involves a change in the system responsible for the transport of sodium ions through the surface membrane. Intracellular microelectrode studies[21] provide abundant evidence to support the viewpoint that quinidine sulfate does interact with cardiac cell membranes in such a way that their selective semipermeability to certain ions is altered. If the properties of the extracted lipids resemble those of the lipids in situ in the membrane-microsomal fractions of intact cardiac muscle cells, then it is possible that the present demonstration of the interaction of quinidine sulfate with the lipid fraction as above may provide the mechanism whereby such a changed semipermeability is produced and may establish the basis for the drug's therapeutic action.

There is considerable evidence that calcium ions are intimately involved in the events associated with excitation-*contraction coupling in cardiac muscle.*[4] Although it is known that depolarization of cardiac muscle cells, including that which is associated with the action potential, is accompanied by an influx of calcium ions,[5] the mechanism whereby these ions penetrate the lipid-containing cell membrane[22] remains obscure. If, as Woolley has suggested,[23] lipids are involved in the transport of calcium ions from the aqueous extracellular phase across the aqueous-lipid interface presented by the intact cell-membrane, then drugs which react with the lipid to impede its calcium-transporting ability may lower the intracellular concentration of ionized calcium. The literature contains many references to the depressant action of quinidine sulfate on cardiac contraction.[23,24] This depressant state possibly could reflect a reduced intracellular concentration of ionized cal-

cium consequent upon the decreased calcium transporting activity of the membrane-microsomal lipids in the presence of quinidine sulfate. In addition it is possible that the antifibrillatory action of quinidine sulfate reflects its ability to interfere with this calcium transporting activity of cardiac cell membrane lipids. Thus Grumbach Howard and Merrill[25] have shown that fibrillation may result from a rapid rise in the extracellular concentration of calcium.

Summary

Lipids extracted from the membrane microsomal fraction of rabbit ventricular muscle were found to facilitate the transport of calcium ions from an aqueous to a lipid solvent (chloroform) phase.

Quinidine sulfate (5 to 100 μg per milliliter) inhibited this lipid facilitated transport of calcium ions, the percentage inhibition varying with the concentration of quinidine sulfate present.

These findings are discussed in terms of the hypotheses that the therapeutic action of quinidine sulfate may involve an inhibitory action on the transport of calcium ions from the aqueous extracellular phase across the lipid-containing cell membrane.

I am deeply indebted to Dr T E Lowe for his continued interest in this project and for his advice during the preparation of the manuscript.

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Effect of nicotine on cardiac necrosis induced by isoproterenol

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It has been previously demonstrated that the administration of nicotine in amounts approximating those obtained from smoking produces significant increases in the incidence of myocardial lesion, lesion severity, and mortality, and a decrease in myocardial potassium in rats given corticosteroid-electrolyte-stress (SSS) treatment. The degree of specificity which this potassium-depleting regimen has for the observed interaction with nicotine is not known, although it has also been demonstrated that rats receiving a hypercholesterolemic diet and small doses of ergometrine respond to chronic nicotine treatment with the production of myocardial lesions which are further characterized by thickening and tortuosity of the small coronary vessel.

In order to evaluate the specificity of the above mentioned interactions, isoproterenol, which is a potent myocardial necrosis-inducing treatment,[5] was substituted for the SSS regimen after the subchronic administration of nicotine. This experiment essentially paralleled the one in which the SSS treatment was used to produce the basic level of necrosis. In addition, nicotine was also chronically administered to separate groups of rats at several dose levels for a period of 6 months prior to the administration of isoproterenol in order to detect possible tolerance to the cardiac effect of nicotine or cumulative effects thereof.

Materials and methods

Female Sprague-Dawley rats which weighed from 80 to 90 grams were given Purina Lab Chow and water *ad libitum*. Ten animals were used for each treatment. The subchronic dose of nicotine consisted of a 2-pack equivalent of nicotine (2.28 mg. per kilogram)[4] administered in the drinking water each day for 7 days prior to the injections of isoproterenol. Chronic administration of nicotine for 6 months was at three dosage levels, namely, 1/8-pack equivalent (0.14 mg. per kilogram per day), 1/2-pack (0.57 mg. per kilogram per day), and 2-pack (2.28 mg. per kilogram per day).

Racemic isoproterenol HCl, 50 mg. per kilogram, was administered subcutaneously to the subchronic nicotine group on the afternoon of the sixth day of treatment; the dose was repeated 24 hours later and the animals were sacrificed by decapitation on the following afternoon. Hearts were graded using a double-blind procedure on a severity scale of 1 to 4

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Table I. Myocardial damage induced by isoproterenol as influenced by subchronic and chronic nicotine

Treatment	*N*	*Per cent mortality*	*Per cent incidence*	*Average severity ± S.E.*	*P**	*Mg./100 mg. dry weight potassium*	*P**
No treatment	10	0	0	0	<0.001	1.469 ± 0.004	N.S.
Isoproterenol control	10	0	90	1.55 ± 0.24	—	1.335 ± 0.065	—
Isoproterenol + nicotine 2 packs (7 days)	10	0	90	1.80 ± 0.24	N.S.	0.837 ± 0.051	<0.001
Isoproterenol + nicotine ¼ pack chronic	10	30	60	1.21 ± 0.48	N.S.	1.451 ± 0.023	N.S.
Isoproterenol + nicotine ½ pack chronic	10	30	100	1.85 ± 0.32	N.S.	1.499 ± 0.018	N.S.
Isoproterenol + nicotine 2 packs chronic	10	20	100	2.56 ± 0.23	<0.01	1.459 ± 0.036	N.S.

*Values of P are in comparison with isoproterenol control.

The concentration of potassium was determined in the dried heart. Details of the methods have been described previously.[1]

Results and discussion

The data presented in Table I indicate that nicotine, in addition to the previously demonstrated interactions leading to or potentiating myocardial necrosis with steroid-salt-stress (SSS) or hypercholesterolemia and ergometrine, also intensifies the response to a third agency, namely, isoproterenol. Similar to the results obtained with the SSS treatment, myocardial potassium was significantly reduced by the acute treatment with nicotine, although mortality, percentage incidence, and average severity were not significantly affected. Furthermore, however, a point of potential importance is that chronic treatment with nicotine followed by isoproterenol did not result in a significant reduction in myocardial potassium, whereas it did increase the average severity of the lesions. Although the average severity of the lesions produced by the isoproterenol treatment was significantly increased only in the group of animals receiving the "2-pack" equivalent for 6 months, and was not increased by the lower chronic doses or by the "2 pack" subchronic dose, there was a progressive increase in the severity of the lesions as related to the size of the chronic doses. The chronic "2 pack" dose not only produced a greater average severity of lesions than that observed in the isoproterenol control (P < 0.01) but also greater than that with the ½-pack dose (P < 0.01) and the ¼-pack dose (P < 0.05).

A lowered myocardial potassium content has been generally observed in corticosteroid and salt-induced cardiopathy,[1] and a potassium deficiency has been shown to condition the myocardium to the effect of other forms of stress.[6] Furthermore, extreme potassium deficiency alone will induce myocardial necrosis.[7] Nevertheless, the specific relationship between myocardial potassium concentration and the production of, or the susceptibility to, necrosis of the heart is still not entirely clear. In some studies no demonstrable correlation was found between the severity of cardiac lesions and the myocardial potassium concentration, whereas in others, data have been reported which were thought to refute the role of potassium deficiency in the production of electrolyte steroid cardiac necrosis.[8] In the latter, cardiac necrosis could not be demonstrated despite low myocardial potassium. A recent investigation has demonstrated that rats without necrosis but having myocardial potassium lowered to the range usually associated with necrosis still had adequate amounts of potassium in the skeletal muscle. It was concluded that the best criteria of changes consistent with the development of myocardial necrosis were potassium and intracellular sodium con-

tent of skeletal muscle and the degree of metabolic alkalosis.

The marked loss of cardiac potassium produced by short term nicotine treatment in conjunction with isoproterenol in the present study was not accompanied by an increase in mortality percentage incidence or average severity of necrosis, yet the same dose of nicotine administered for 6 months although not affecting cardiac potassium caused a marked increase in the average grade of severity of lesions. It is speculated that an explanation for the effects of the short term nicotine treatment may be related to the inadequate development of necessary ancillary conditions, i.e. low skeletal K and (or) metabolic alkalosis. An explanation for the lack of lowered myocardial potassium when the average grade of severity of lesions was significantly elevated by chronic nicotine and isoproterenol is not so easily explanable although it suggests that myocardial potassium may be restored to normal levels under conditions of chronic nicotine administration while other necrosis-inducing factors, perhaps not directly related to the level of potassium are enhanced.

Since a previous study using the steroid salt stress (SSS) regimen[1] had demonstrated an increase in the severity of lesions after short term (7-day) administration of nicotine it is clear that additional predisposing or nicotine interacting factors are found in the nicotine SSS treatment that are not produced by the short term nicotine-isoproterenol treatment as employed. For with the latter no nicotine induced increase in the severity of the lesions resulted despite the fact that the average severity of the lesions was higher than that previously reported for SSS ($P < 0.05$).[1]

Summary

The average severity of myocardial lesions produced by the injection of isoproterenol was not increased by the prior administration of "2 pack equivalents" (2.28 mg. per kilogram) of nicotine per day for 7 days. The administration of the same dose of nicotine for 6 months resulted in a significant ($P < 0.01$) increase in the average severity of isoproterenol induced lesions. Smaller amounts of nicotine administered chronically ("¼-pack" or 0.14 mg. per kilogram and "½-pack" or 0.57 mg. per kilogram equivalents) did not increase the average severity of the lesions. The lack of a consistent relationship between lesion severity and myocardial potassium content is discussed.

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Pulmonary vascular compliances and filtrations

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The volume of blood in the pulmonary vessels is an important determinant of the effectiveness of utilization of the respiratory surfaces for gas exchange. This volume varies with the number of pulmonary vessels, their transmural pressures, unstressed volumes, and compliances. If these characteristics of the pulmonary vasculature could be determined several aspects of respiratory and cardiovascular function might be clarified.

The anatomy and mechanics of the lung introduce special problems into the estimation of the pulmonary vascular volume.[1] For example, although the pressure in the airways is approximately at atmospheric levels, the transmural pressures in the intra-alveolar vessels increase significantly from the most elevated portion of the lung to its most dependent portion. Transmural pressure is also affected by the surface tension at the air liquid interface of the alveolar membranes, the osmotic pressure of the blood proteins, differences in pressure in the airways due to inhomogeneous ventilation and the oscillations produced by the ventilatory and cardiac pumps.

In addition two discrete pulmonary vascular transmural pressures must be considered the intralobar and the extralobar. The intralobar (airway) pressure is the ambient pressure for the alveolar capillaries and perhaps for some of the smaller arteries. The extralobar (pleural) pressure is the ambient pressure of the larger arteries and veins. The transpulmonary (airway minus pleural) pressure, which affects the volume contained within the lung may also be expected to modify the size shape, and length (geometrical relationships) of its vessels.

Although numerous investigators have examined various combinations of some of these factors,[2-4] these analyses have been incomplete since one or more of the pulmonary factors noted above were not completely controlled. For example, the effect of pleural pressure on the pulmonary vessels has been virtually neglected. Some of the investigations have examined the effects of abnormally large differences in pressure thereby ignoring the fundamental consideration that the pressures operative on pulmonary structures are normally of the order of only a few millimeters of mercury.

In the present study the effects of small differences in pressure on the pressure volume relationships of the intralobar and extralobar pulmonary vessels have

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Fig. 1. The lung lobe, shown as the lobulated structure, is enclosed in the bottle (square). The arterial pressure reservoir ($P_{arterial}$) (black) is set at a selected level to generate the pulmonary vascular pressure. The venous system is clamped off in the present study. The transpulmonary pressure ($P_{transpulm}$) is the difference between the pressure in the airways (P_{airway}) and the pressure in the pleural space ($P_{pleural}$). Displacement of fluid out of or into the intralobar (airway) compartment or the extralobar (pleural) compartment are indicated by movement of indicator ball in the horizontal tubes connected to each of these compartments. (All systems are filled with saline.)

been determined in the isolated lung lobe of the dog under conditions in which osmotic, hydrostatic, and surface forces as well as geometrical relationships were controlled.

Methods

Five dogs of 12 to 28 kilograms of body weight were anesthetized with intravenous sodium pentobarbital (30 mg. per kilogram) and heparinized (2 mg. per kilogram). After hyperventilation with pure oxygen for 15 minutes using positive pressure respiration, the trachea was occluded while the pulmonary blood flow degassed and collapsed the lung.[7] The chest was opened and the left lower lobe of the lung was removed. Saline-filled cannulas were tied into the bronchus of the lobe and into its pulmonary artery and vein (Fig. 1).

To wash the vascular bed free of blood, 100 ml. of 0.9 per cent saline was perfused from artery to vein, and then 100 ml. of saline was perfused from vein to artery. The lobe was immersed in a "pleural" bottle of saline. Cannulas in the artery, vein, and bronchus and in the pleural space were each connected with glass tubes which passed through a rubber stopper. The stopper was sealed tightly in the mouth of the bottle. Care was taken to exclude air from the system.

The arterial, venous, bronchial, and pleural cannulas were connected to reservoirs which were maintained at selected constant levels, open to the atmosphere. To maintain constancy of pressures in the airway and pleural compartments despite changes in volume, these compartments were connected to saline-filled glass tubes 1 meter long, which dipped into reservoirs which were connected by siphons

Fig. 2. Siphon arrangement for maintenance of constant pressure. Horizontal tube A is connected at left (not shown) with the horizontal tube from the pleural or airway compartment of Fig. 1. Tube A containing the indicator ball dips into reservoir B. The level of fluid of B is the zero reference level of the system. Siphon C connects reservoirs B and D. Overflow from D is collected in funnel E, which empties into Reservoir F. Pump G raises fluid from F through pipe H to reservoir D. Because of the continuous overflow of D, fluid can move into A from either direction without change in reference pressure or entry of air into the system.

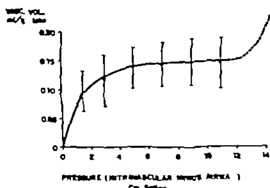


Fig 3 Transmural pressure and displacement from the airway Displacement from the airway in milliliters per gram of wet lung is given in the vertical axis vascular minus airway pressure in centimeters of saline is given in the horizontal axis. Airway pressure is the zero reference level. At vascular pressures lower than airway pressure (*not shown*) there was no displacement of fluid into the airway compartment. Displacement of fluid from the airway compartment began when the rising vascular pressure equaled and then exceeded airway pressure The displacement volume increased to a plateau as vascular pressure was about 4 cm. of saline. The vertical lines give the standard deviations for series of 12 tests at each level of pressure in five lobes. When intravascular pressure was 13 cm. or more above airway pressure the rate of displacement from the airway space was so rapid that it could not be measured this is indicated by the dotted line

to secondary overflow reservoirs (Figs. 1 and 2) Movements of fitted plastic indicator balls in the horizontal tubes marked the simultaneous volumes of displacement of fluid from or into the airway or pleural spaces. The levels of the overflow reservoirs determined the pressures in the airway and in the pleural spaces Vascular pressure was controlled by varying the height of the reservoir connected to the arterial cannula. The venous cannula was occluded Movement of fluid in the vascular bed was limited to filling of the vessels of the lobe from the arterial side

Since changes as small as 1 mm of saline pressure or 0 1 ml of volume could be measured with accuracy the pulmonary vascular compliances (Δ volume Δ pressure) at various levels of pressure could be established By using saline to fill the airway and pleural spaces as well as the blood vessels, surfactive,[8-10] osmotic and hydrostatic effects[11] were obviated By holding the transpulmonary pressure constant and at less than 5 cm of saline, the degree of elongation of the elements of the lung parenchyma and of the blood vessels was controlled.

Studies reported separately show that the lobe prepared as described above is

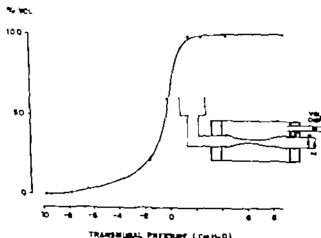


Fig 4 Displacement of volume into a segment of latex rubber (Penrose) tubing as transmural pressure is varied Penrose tubing of 1.3-cm. diameter and 14.5-cm. length was fitted over glass connectors and sealed in a glass cylinder as shown in the insert One end was clamped off A reservoir P applied vascular pressure The volume displaced was measured as in Fig 2 The vertical axis gives volume in per cent of maximal. The maximal volume in the segment was 16 ml The horizontal axis gives transmural (intravascular minus extravascular) pressure As intravascular pressure (P) is raised from approximately −10 cm of saline the volume of fluid entering the soft-walled vessel is small until transmural pressure approaches zero. At approximately zero transmural pressure small differences in pressure produce large increments in volume in vessel volume When the unstressed volume is filled, higher transmural pressure produces little further increment in volume Compare with Fig 3

responsive to physiologic doses (0.1 μg or less per gram of lung) of acetylcholine histamine serotonin or adrenalin.[13]

Results

Several experimental approaches were used to determine the effects of arterial pleural and airway pressures on the displacement of fluid from or into the airway and pleural compartments. A number of complex relationships appeared in the data, with families of curves which varied depending on the settings of the airway or pleural pressure. The data could be analyzed most satisfactorily by considering the phenomena in terms of vascular transmural pressures.[13] The zero reference level for the vessels inside the airway was the airway pressure, the zero reference for the vessels exposed to the pleural fluid was the pleural pressure.

Airway compartment. Changes in arterial pressure from −10 to 0 cm. of saline (with respect to airway pressure) resulted in no displacement of fluid out of the airway compartment.

RAPID DISPLACEMENT. As arterial pressure exceeded airway pressure a discrete volume of saline was displaced from the airway within a few seconds; the volume displaced increased progressively with each increment to a maximum of approximately 14 per cent of the empty lung weight at a vascular pressure of about 4 cm. of saline. Further elevations of vascular pressure to 13 cm. of saline produced only slight displacement of saline out of the airway (Fig. 3).

Displacement of volume into a segment of Penrose tubing as vascular pressure was increased was rapid and essentially of the same form (Fig. 4) as the change in volume in the airway compartment. Thus the displacement of volume as the vessel pressure, P_V, was raised to the level of the Penrose segment was small. As the transmural pressure became positive the Penrose segment filled completely within a range of 4 cm. of water pressure. Further increases in P_V had no significant further effect on volume in the segment.

CONTINUOUS DISPLACEMENT. At vascular pressures above 13 cm. of saline displacement of fluid from the airway was continuous at rates which could not be measured with the present apparatus, and which persisted for test periods of more than 7 minutes.

Pleural compartment. Analysis of the data accumulated in 10 series of tests on 5 lung lobes indicated that all of the tests on the pleural compartment could be rendered comparable by using the pleural pressure as the zero reference level.

The pleural indicator responded in two phases to increments in vascular pressure. Immediately after each elevation of the arterial pressure, there was a *rapid* displacement of fluid from the pleural space which was completed within 1 minute (Fig. 5). After completion of each rapid phase a *continuous* displacement continued for as long as 20 minutes (Fig. 6).

The rapid phase of displacement of fluid from the pleural compartment was evident in all experiments (Fig. 5). The rate of displacement of fluid from the pleural compartment during the rapid phase per unit of rise in vascular pressure was constant, except as noted below at approximately airway pressure values. Tests could not be carried out at transmural pressures greater than 15 cm. of saline because of the excessively rapid displacement from the airway. The rate of the continuous phase of displacement from the pleural compartment was proportional to the pleural transmural vascular pressure (Fig. 6).

When the rising vascular pressure equaled and then exceeded the airway pressure (Fig. 7), an increment of displacement from the pleural compartment of about 0.07 ml. per gram of lung was noted. This appeared to be due to filling of the venous system as previously collapsed capillaries were filled and fluid from the arterial bed could then enter and fill the extralobar venous system.

LUNG INFLATION. The pleural vascular compliance was not affected significantly by changes in the degree of inflation of the lung (Fig. 8). Thus a change in the volume of the lung produced by lowering the pleural pressure from 3 to 5 cm. of saline below airway pressure resulted only in a shifting of the pleural displacement tracing. There were no effects on the pattern of displacement of fluid from the airway compartment (Fig. 8).

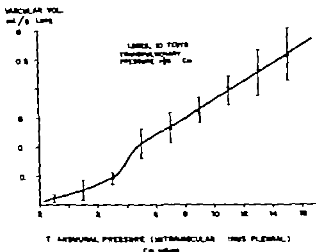


Fig. 5. Transmural pressure and rapid displacement from the pleural compartment. The vertical axis gives vascular volume in milliliters per gram of lung. The horizontal axis gives transmural (intravascular minus pleural) pressure. Vascular volume was zero when transpulmonary (airway minus pleural) pressure was −3 cm. and vascular pressure was −2 cm. As vascular pressure was raised progressively, the transfer of fluid into the lung lobe was nearly linear prior to about 3 cm. of saline. Between 3 and 5 cm. of saline an amount of fluid equal to approximately 0.07 mL per gram of lung suddenly entered the vascular bed; this effect may be due to filling of the venous system as vascular pressure exceeds airway pressure. Further increments in intravascular pressure produced a nearly linear increase in pleural vascular volume. The vertical lines give the standard deviations.

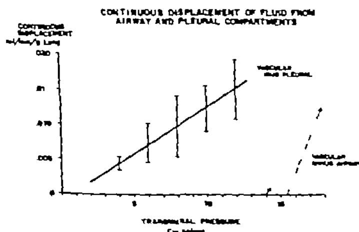


Fig. 6. Filtration of saline from the vascular bed into airway or pleural compartments. The vertical axis is the filtration rate in milliliters per minute per gram of wet lung weight. The horizontal axis is the transmural pressure. Filtration across the pleural vascular membrane (*line at left*) begins approximately at 0 cm. The filtration rate into the airway is zero up to approximately 13 cm. of saline above airway pressure; the broken line and the arrow at approximately 15 cm. of saline indicate that filtration is so rapid that it could not be measured accurately with the present apparatus.

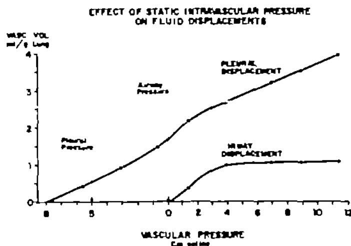


Fig. 7. Relationship between the volume displaced from the intralobar and extralobar vascular beds (*vertical scale*) plotted against the transmural (vascular minus airway) pressure in centimeters of saline (*horizontal scale*). Airway pressure was the intralobar zero reference level. At vascular pressures less than zero, no fluid was displaced from the airway. Displacement of fluid from the airway began when vascular pressure was raised to airway pressure. At 4 cm. of saline 0.14 ml. per gram of wet weight of the lobe had been displaced from the airway. Further increases in vascular pressure up to 12 cm. of water had no significant effect on displacement from the airway compartment. In the experiment given, pleural pressure was 5 cm. lower than the airway pressure. As vascular pressure was increased from −8 cm. of saline extralobar volume increased almost linearly up to +12 cm. of saline except for a slight increase in volume as the level of airway pressure was crossed. This extra volume of fluid entering the vascular bed at zero airway pressure as the arterial level was being elevated appears to have been due to filling of the venous system which had been emptied prior to the experiment. Discussed in text.

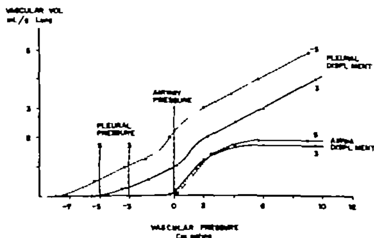


Fig. 8. Effect of transpulmonary pressure on intralobar and extralobar vascular displacements. The vertical axis gives vascular volume in milliliters per gram of lung; the horizontal axis gives vascular pressure. Two different transpulmonary pressures are illustrated. The displacement from the airway compartment was essentially the same at transpulmonary pressures of 5 and 3 cm. of saline. Pleural displacement was unaffected when considered in terms of its transmural (vascular minus pleural) pressure. A sharp increase in pleural displacement occurred as vascular pressure was elevated to airway pressure.

Discussion

Problems in pulmonary vascular compliance. The suspension of the capillaries in the air filled lung produces a range of transmural pressures which decrease with the degree of elevation of each capillary. At a given pulmonary vascular pressure the filling of each vessel varies with its transmural pressure. Thus, the compliance of these vessels can vary over a wide range from the lower to the more elevated portions of the lung.[1,31] If such a system is partially filled with blood, saline, or other liquid, compliance will vary with the size of the lung, its degree of inflation, the airway and pleural pressures, and the intravascular pressures. The effects produced by varying transmural pressures can be eliminated by filling the airway with saline.[4,8]

When, for experimental purposes, the lung is suspended in air, the normal balancing effect of the pleural fluid on the pleural vessels is lost and an abnormal hydrostatic gradient comes into operation. By placing the lung in a saline bath, this abnormal pleural pressure gradient is eliminated.

Inflation of the lung elongates the pulmonary parenchyma and its vessels. The effects of such elongation on the caliber, length, and volume of these vessels has not been previously clarified. On the basis of plastic injections, Burton and Patel[1] suggested that inflation reduces the kinkiness or gnarliness of the pulmonary arterial bed. The present technique which holds the size of the lung constant and therefore controls the geometrical relationships of the vessels indicates that inflation of the lung within the ranges examined had no effect on the intravascular volumes of either the intralobar or extralobar vessels (Fig. 8).

Surfactive materials can modify the alveolar contours,[9-11] and perhaps through this the state of filling of the alveolar capillaries, thereby complicating the analysis of pulmonary vascular volume. Despite the physiologic nature of blood as a vascular perfusate,[24] it complicates the estimation of the pulmonary vascular volume because the osmotic forces of the plasma can modify the degree of hydration of the capillary wall and the alveolar surface. The air fluid interface, the surface forces and the osmotic forces are controlled by filling the airway with saline.[4,9,16,17] It must be noted that the saline bath used in our experiments may also affect the pulmonary structures.

Zero reference levels used by various workers have included the top or base of the lung lobe, or the hilar level. The present findings show that the behavior of a given vessel varies with its transmural pressure. In the present study, the zero reference level for the intralobar vessels was the airway pressure, whereas the zero reference for the vessels facing the pleura was the pleural pressure.

The airway pressure oscillates several centimeters of water during normal ventilatory activity, and even more in abnormal ventilation. Results of studies in which the airway pressure is not recorded may, therefore, vary with the uncontrolled transmural pressures acting on the vessels of the airway.[2,3,8,14,19]

The use of stable airway, pleural, and vascular pressures, as in the present study, provides the basal conditions necessary for the evaluation of the variables under examination. The results show that the pulmonary vascular bed consists of two discrete segments: (1) intralobar (airway) and (2) extralobar (pleural), each of which exhibits quite different characteristics of elasticity and permeability.

Vascular compliance in the airway. The airway compartment contains the alveolar capillaries and their immediately connecting vascular segments. The present data indicate that, when airway pressure exceeds vascular pressure, the vessels facing the air spaces are probably collapsed. As a rising vascular pressure equals and then exceeds the airway pressure, the vessels in the airway fill and displace an equivalent volume of fluid from the airway.

In the course of a rise in intravascular pressure of only 4 cm. of saline above the airway pressure, a volume of saline equal to about 14 per cent of the weight of the empty, wet lung lobe was displaced from the airway space (Figs. 3, 7, and 8), presumably as a result of the complete filling of the previously collapsed alveolar capillaries. Further elevation of the vascular pressure up to 13 cm. of saline further displacement of fluid

airway These data indicate that the alveolar capillaries, although collapsible are relatively nondistensible at least within this range of pressure The absence of a continuous displacement of fluid from the airway when transmural pressure is less than 13 cm of saline indicates a threshold which must be exceeded before filtration into the lobes of the lung begins Hughes May and Widdicombe[24] observed that pulmonary edema did not occur at perfusion pressures of less than 21 cm of Ringer Locke's solution these workers used an airway pressure of 7 cm of water It may be suggested that the difference of 14 cm of water was the filtration threshold in their experiments

This threshold could provide a margin of safety in keeping the airway dry thereby facilitating gas exchange

The remarkably high rate of continuous displacement of fluid from the airway at transmural pressures higher than 13 cm of saline (Fig 3) suggests that the vessels of the airway may become aneurysmal and thinned with increases in their permeability Hydrophobic (surfactive) materials on the alveolar surface may play a role in this threshold

A positive transmural pressure of 4 cm of saline fills the airway capillaries with 0 14 ± 0 04 ml of fluid per gram of empty lung weight (Fig 3) In man pulmonary capillary volumes based on the diffusion method are stated to range from 50 to 100 ml per square meter of body surface,[25,26] increasing to 150 ml during exercise.[24,26,27]

Wearn[28] observed that the pulmonary capillaries may be in either the open or closed state. Lewis[29] and Rosenburg[21] using the carbon monoxide diffusion method for the estimation of capillary volume in exercise, came to the same conclusion Our studies indicate that the opening and closing of capillaries may be accounted for on the basis of very small changes in transmural pressure

Pleural vascular compliance The rapid phase of displacement of fluid from the pleural compartment which occurred immediately on each change in vascular pressure increased approximately linearly with the vascular-pleural transmural pressure difference. This effect appears to represent filling of pulmonary vessels exposed to the pleural surface Since changes in vascular pressure in ranges lower than pleural pressure result in displacement of fluid out of or into the pleural compartment some extralobar vessels appear to resist collapse The relatively high pressure in the main pulmonary arteries prevents collapse of these relatively thick walled vessels As blood leaves the alveolar capillaries and crosses the alveolar boundary to enter the venules, it courses in the interlobular septa (Fig 1) to enter the lower pressure environment of the pleural space. In this site the transmural pressure is more positive and the filled veins provide minimal impedance to outflow from the alveolar capillaries. Such an arrangement facilitates the movement of blood out of the alveolar capillaries and thereby diminishes the likelihood of transudation into the airway spaces

The finding that the vessels facing the pleura may fill partially even when pleural pressure exceeds intravascular pressure indicates that the pulmonary venous system is supported against potential collapse, possibly by elastic fibers which attach the adventitia to adjacent pleural structures. Such anatomic arrangements would have functional value in the pulmonary venous system since it would militate against collapse of the extralobar vessels.

In the present technique the alveolar capillaries remain collapsed and filling of the venous system is prevented as long as airway pressure exceeds arterial pressure As the rising arterial pressure equals airway pressure the capillaries open partially and some flow through them enters the vascular bed The sharp displacement of fluid from the pleural compartment as the rising arterial pressure becomes equal to the airway pressure may represent the entry of fluid into the previously relatively empty venous bed (Figs 5 7 and 8) These data suggest that the unstressed venous volume is approximately 0 07 ml per gram of empty wet lung lobe.

Pleural filtration Although the potential mechanisms of pulmonary edema have been examined by many workers,[30,31,32] few studies of the transfer of fluid into the pleural space have been made Trans-

fer of fluid from the pulmonary vessels to the pleural space is considered to be a reflection of the pleural vascular transmural pressure.[34-37]

The continuous displacement of fluid from the pleural compartment in proportion to the difference between vascular and pleural pressures suggests that this represents the filtration of fluid from the vascular bed to the pleural space. The fall in pressure after injection of fluid into the venular bed of the isolated lung has sometimes been attributed to stress relaxation[7] of the vessels. However, this effect may have represented filtration into the pleural and airway spaces.[33,34]

The occurrence of filtration from the vascular compartment to the pleural compartment in proportion to the pleural transmural vascular pressure suggests that a large permeable surface area of the vascular bed is in contiguity with the pleural space. This surface may represent the downstream junction of the pulmonary capillaries with the venules and may account for the transfer of ultrafiltrate from the vessels to the pleural compartment.[34-37] The presence of a drainage system from the venular end of the capillaries to the pleural space would be indicated. The continuous movement of the pleural volume indicator may be considered to reflect a resultant of the product of the pressure gradient from vascular bed to pleural space, the filtration coefficient of the membrane, and the surface area available for filtration. The present technique provides a basis for quantification of these parameters.

Summary

In 13 experiments on lung lobes of 5 dogs hydrostatic, osmotic, and surface forces were eliminated by filling the vascular bed and the airway and pleural compartments with saline, with care being taken to maintain an air-free system. As vascular pressure was varied, displacements of fluid from the intralobar compartment and from the extralobar compartment were measured separately. There was no displacement from the intralobar (airway) compartment until vascular pressure equaled and exceeded airway pressure. Over the course of the next rise in arterial pressure of 4 cm. of saline approximately 14 per cent of the weight of the empty wet lung lobe was displaced from the intralobar compartment. This is considered to be the filled unstressed volume of the alveolar capillaries. Further elevations of vascular pressures had no effect on airway capillary volume or on filtration into the air spaces, until vascular pressure reached 13 cm. of saline above airway pressure; at pressures higher than 13 cm. of saline a considerable and continuous displacement occurred. This is considered to be due to transcapillary filtration of fluid. These results indicate that the intralobar vessels (alveolar capillaries) are nondistensible, collapsible, impermeable channels. The vessels become permeable at a transmural pressure of about 13 cm. of saline.

As vascular pressure was raised, the extralobar displacement was nearly linear over a range from −8 to +15 cm. of saline (pleural pressure = 0). Filtration into the pleural space was proportional to the vascular minus pleural pressure. The extralobar vessels are characterized as permeable, distensible, noncollapsible conduits.

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Case reports

Vibrio fetus endocarditis

Report of 2 cases

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Vibrio fetus is an important cause of infectious abortion in cattle and sheep. Human infection with *V. fetus* is uncommon but is being recognized with increasing frequency. We have observed 2 patients with subacute bacterial endocarditis due to *V. fetus* within 1 year. Only 3 other cases have been recorded previously in the medical literature.[1-3] Since infection with *V. fetus* responds readily to appropriate antibiotic therapy, it is important that this organism be considered in all cases of bacterial endocarditis. In this paper we shall record the case histories of our 2 patients, review the epidemiology and clinical manifestations of the infection, and describe laboratory methods for the isolation and identification of *V. fetus*.

Case histories

Case 1. A 67-year-old white man, a former boxer and construction laborer, was admitted to Cook County Hospital in November 1963. He was mentally confused and unable to give an accurate history. He complained that he had had fever, chills, nausea, diarrhea, poor appetite, and loss of weight for 7 weeks, and a rash on his arms and legs for 2 weeks. In the past he had had hypertension, occasional ankle edema, paroxysmal nocturnal dyspnea, and nocturia. Three years ago he was treated for pulmonary tuberculosis in a sanitarium. He drank alcohol liberally.

Physical examination revealed a cachectic, dehydrated, pale white man who appeared to be both chronically and acutely ill. The blood pressure was 90/70 mm. Hg, pulse 88 per minute, respiration 24 per minute, and temperature 97°F. A confluent petechial and purpuric eruption was present on the hands, feet, and back. The mucous membranes were pale. There were no subungual hemorrhages or clubbing of the fingers. There were no conjunctival hemorrhages or icterus. The fundi appeared to be normal. The tongue was smooth and beefy red. The eyes, ears, nose, and throat were otherwise normal. The neck was supple. The thyroid gland was not palpable. There was moderate distention of the neck veins. There was no peripheral lymphadenopathy. The thorax was symmetrical, and the lung fields were hyperresonant to percussion. The breath sounds were diminished, but scattered rhonchi were audible in all areas. The heart size was normal to percussion, and the rhythm was regular. The heart sounds were distant and obscured by respiratory rhonchi. No murmurs were heard. The abdomen was slightly distended and there was tenderness in the right upper quadrant, but no muscle

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guarding. The liver was enlarged and extended 4 cm. below the right costal margin. No other organs or masses were palpated. There was no evidence of thrombophlebitis. Slight pitting edema of the legs was present. The genitalia were normal. The neurological examination showed disorientation to time and place but was otherwise normal.

LABORATORY INVESTIGATIONS. The urinalysis showed specific gravity 1.010, protein 2+, white blood cells 5-10 per high-power field, erythrocytes 5-10 per high-power field, and was otherwise normal. On admission, the hematocrit was 19 per cent and the erythrocyte sedimentation rate was 80 mm. per hour. The next day the hemoglobin was 4.9 Gm. per 100 ml., red blood cells 1,930,000, and white blood cells 21,550 per cubic millimeter. The differential white cell count showed segmented cells 56 per cent, bands 36 per cent, lymphocytes 4 per cent, monocytes 2 per cent, and metamyelocytes 2 per cent. The blood film showed a decrease in platelets and 2+ anisocytosis, polychromatophilia, and toxicity. A platelet count showed 10,000 platelets per cubic millimeter. The reticulocyte count was 2 per cent. Aspiration of the bone marrow showed moderate hypercellularity. The megakaryocytes were decreased in number. The nucleated RBC: WBC ratio was 1:1. Erythropoiesis was normoblastic, and granulopoiesis was moderately toxic. There was an increase in histiocytes and reticular cells. Occasional giant band cells were seen.

Biochemical determinations showed a blood urea nitrogen of 89 and creatinine of 4.0 mg. per 100 ml. The total protein was 5.3, albumin 2.9, globulin 2.4, and gamma globulin turbidity 2.02 Gm. per 100 ml. The calcium was 8.3 and phosphorus 5.6 mg. per 100 ml. The sodium was 123, chloride 80, potassium 3.0, and CO_2 16.0 mEq. per liter. The total cholesterol was 98 mg. per 100 ml., with 56 per cent esters. The icteric index was 9 units, the alkaline phosphatase was 3.6 Bodansky units, the cephalin flocculation was 2+, and thymol turbidity was 6.7 MacLagen units. The glucose was 118 mg. per 100 ml. Roentgenograms of the chest showed the heart to be of normal size and configuration. The aorta was elongated and the arch was calcified. The electrocardiogram showed low voltage, a sinus tachycardia, and nonspecific flattening of the T waves in Leads I, V_{4-6}. The Kahn test was negative. A skin test with O.T., 1:1000 dilution, was negative. Smear and culture of one collection of sputum was negative for *Mycobacterium tuberculosis*.

On admission the patient was given intravenous fluids and large doses of vitamin C and thiamine. The day after admission he was semicomatose and appeared to be moribund. His blood pressure was 105/60 mm. Hg, pulse 120 per minute, and temperature 101°F. He was given 1,000 ml. of whole blood, hydrocortisone 300 mg. daily, and antituberculosis therapy with isoniazid, 300 mg. daily, and streptomycin, 1 Gm. daily, was begun. On the third hospital day, six samples of blood for culturing were drawn and therapy with intravenous penicillin, 15 million units daily, was instituted. On the fifth day, many coarse râles were heard throughout the chest. In the afternoon he had a massive epistaxis, which was controlled by a posterior nasal pack. From then on his condition deteriorated. His output of urine decreased. The blood urea nitrogen rose to 100 mg. per 100 ml. and he lapsed into a coma. He died 8 days after admission to the hospital, having been ill for approximately 8 weeks.

Postmortem examination revealed the following: marked cachexia, hypertrophy of the heart, an unruptured aneurysm of the sinus of Valsalva, verrucous endocarditis totally involving the left anterior aortic cusp and partially infiltrating the right anterior cusp, tiny verruca on the mitral valves, severe massive bilateral bronchopneumonia, and tracheobronchitis.

After the patient died, *V. fetus* was cultured from all specimens of blood drawn during life. The identity of the organism was verified by Miss Elizabeth O. King, of the Communicable Disease Center, Chamblee, Georgia. *V. fetus* organisms were not recovered from postmortem cultures.

COMMENTS. The patient presented as a debilitated alcoholic with multiple vitamin deficiencies, severe anemia, thrombocytopenia, and sepsis. Therapy with large doses of penicillin and streptomycin was ineffective. Thrombocytopenia has not been reported previously in infection with *V. fetus*.

Case 2. A 49-year-old unmarried Negro man, a cab driver, was admitted to Cook County Hospital in September, 1964, complaining of chills and fever. Four weeks prior to admission, after a 1-day episode of transient pain in both flanks and a generalized muscular aching, the patient noted heat, pain, and tenderness in a small area on the medial aspect of his left thigh. A roentgenogram of the thigh made at another hospital showed no abnormality. Several days later he developed shaking chills and fever. His temperature was 104°F. He was given an oral medication by his physician, and the symptoms abated temporarily but recurred and persisted for 2 weeks before his admission to the hospital. He also complained of anorexia, loss of weight of 20 pounds, frontal headache, and two recent episodes of vomiting. There was no history of cough, chest pain, hemoptysis, dyspnea, ankle edema, hematuria, upper respiratory infection, or diarrhea. He had not undergone any dental procedures recently. He had no contact with animals. He smoked a moderate number of cigarettes daily and did not drink alcohol. When he was 12 years old he had been told that he had a "heart condition." He was never told that he had rheumatic fever, and there was no history of congestive heart failure. When the patient was 27 years old, he had been rejected for service with the armed forces because of a heart murmur.

Physical examination revealed a well-developed, well-nourished Negro man who did not appear to be chronically ill and was in no acute distress. The blood pressure was 100/40 mm. Hg, pulse 72 per minute and regular, respiration 24 per minute, and temperature 104°F. One suspicious conjunctival petechia was observed. The neck veins were not distended. Examination of the head and neck revealed no other abnormalities. The thorax was symmetrical. The lung fields were clear to auscultation and percussion. On percussion, the cardiac apex was in the fifth intercostal space at the left anterior axillary line. Palpation showed an active left ventricular impulse. On auscultation, there was a soft sys-

tolic ejection murmur and a long diastolic blow at the third intercostal space just to the left of the sternum. Examination of the abdomen showed a sharp edge to the liver one fingerbreadth below the right costal margin. No other organs or masses were palpated. Rectal examination showed a small prostate gland. The stool benzidine test was negative. Examination of the extremities showed a palpable thrill and audible bruit over the lower medial aspect of the left thigh. The blood pressure of the right leg was 170/50 mm. Hg and that of the left leg was 100/50 mm. Hg. Compression of the aneurysm caused no change in pulse rate or peripheral blood pressure. The peripheral arterial pulses were bilaterally equal. There were no signs of inflammation. There was no tenderness of the calves, and Homan's sign was negative. There was no edema. Examination of the genitalia showed that the testicles were of normal size and consistency. The neurological examination was normal.

LABORATORY INVESTIGATIONS. The urinalysis showed specific gravity 1.017, pH 5.0, trace of urobilinogen, 6 white blood cells per high-power field, and was otherwise normal. Cultures of the urine revealed no growth. The hemogram showed a hemoglobin of 11.8 Gm. per 100 ml., erythrocytes 4,120,000 and white blood cells 15,100 per cubic millimeter. The differential white cell count was: segmented cells 78 per cent, bands 5 per cent, lymphocytes 13 per cent, and monocytes 4 per cent. The blood film showed 1+ anisocytosis, rouleaux formation, 2+ toxicity, and normal platelets. Biochemical studies showed a blood urea nitrogen of 19, glucose 70, and uric acid 8.3 mg. per 100 ml. The total protein was 7.8, and gamma globulin turbidity was 2.68 Gm. per 100 ml. The alkaline phosphatase was 3.4 Bodansky units, thymol turbidity 6.3 MacLagen units, and cephalin flocculation test was 3+. The antistreptolysin-O titer was less than 1:50. The "C" reactive protein reaction was 3+. The Kahn test was negative. Roentgenograms of the chest showed moderate increase in the transverse diameter of the heart, with prominence of the left ventricle and the aorta. An electrocardiogram showed left ventricular hypertrophy.

The initial therapy of tetracycline, 2 Gm., was discontinued after 1 day. Five samples of blood for culturing were drawn within 48 hours after admission. On the second hospital day therapy with penicillin, 20,000,000 units daily intravenously, streptomycin, 2 Gm. daily intramuscularly, and probenecid, 2 Gm. daily was begun. On the sixth hospital day a purpuric eruption was observed on both supraclavicular fossae and the left thigh, which persisted 2 days.

All five blood cultures grew V. fetus which was sensitive to penicillin, chloramphenicol, tetracycline, erythromycin, and methicillin using the disk method. One of the cultures also grew hemolytic *Staphylococcus aureus* which was coagulase positive. The identity of the V. fetus was subsequently verified by Miss Elizabeth O. King. On the seventh hospital day, therefore, therapy with tetracycline, 2 Gm. a day, was reinstituted in addition to penicillin. A low-grade fever which had persisted for a week now subsided, and the patient became asymptomatic. A sample of blood drawn for culture on the ninth hospital day, while he was receiving antibiotic therapy, showed no growth. On the seventeenth hospital day the patient left the hospital and discontinued all therapy against medical advice.

One month later the patient was observed at the outpatient clinic in response to a letter. He was short of breath on exertion and occasionally noted a rapid beating of the heart, but was otherwise well. He had not returned to work. On physical examination, the aneurysm of the left thigh was no longer demonstrable. The cardiac findings were unchanged. A blood culture showed no growth.

Agglutinating antibodies in the patient's serum were detected against V. fetus organisms isolated from the patient in titers of 1:10 and 1:20 on the ninth and fifteenth hospital day and were negative 1 month later. A higher titer may have been reached during the period that the patient was lost from observation.

COMMENTS. The patient's underlying heart lesion was rheumatic aortic valvular disease. Upon this was superimposed an endocarditis due to V. fetus. The initial manifestation of the infection was a mycotic aneurysm of the femoral artery. Although V. fetus was sensitive to penicillin in the test tube, penicillin was clinically ineffective and the patient did not respond to therapy until tetracycline was administered.

Previously reported aspects of Vibrio fetus infection

Epidemiology. The epidemiology of V. fetus infection in animals has been reviewed by King.[1] In cattle, the infection is a venereal disease. In the bull the organism is found on the prepuce and in the semen. It is apparently maintained indefinitely in the testes. In the cow, there are minor lesions in the vagina. The major lesion is in the placenta, causing interference with the circulation and a resulting abortion. In sheep, ewes are probably infected by the ingestion of contaminated food or water and although venereal transmission may occur, it is relatively uncommon. The guinea pig and hamster can be infected experimentally with V. fetus, after which the disease is spread to other members of the colony by sexual contact.

The epidemiology of human infection with V. fetus is not clear. Twenty-seven cases have been recorded in the literature.[2-20] Whether transmission is by coitus, contact with infected animals, or ingestion of contaminated food and water has not been definitely determined. Hood and Todd[3] have reported an abortion due to V. fetus infection, in which case the organism was isolated from the brain of the fetus and the placenta, and antibodies to

V. fetus were demonstrated in the blood of both parents. This strongly suggests that venereal transmission of the infection had occurred. A similar mode of transmission may have been involved in 3 patients in whom the infection was associated with problems of pregnancy,[4] and in one report of *V. fetus* meningitis in a newborn child.[8] However, virtually all other instances of infection with *V. fetus* have occurred in adult men. The occupation of some of these men could have brought them into contact with infected animals, but many had no contact with animals at all. Although yet to be documented, it seems to be likely that the infection in these patients was by the ingestion of contaminated food and water. The onset of the disease after dental procedures in 2 patients supports the concept that infection may occur by the oral route. The direct transmission of the infection from laboratory culture to skin has also been reported.[7]

Bacteriology. The bacteriologic isolation and identification of *V. fetus* is not difficult if the bacteriologist is aware that this organism is pathogenic for man. The organism is microaerophilic and grows well in tryptone soy broth and tryptone soy blood agar plates under increased carbon-dioxide tension. Primary isolation may require 4 to 5 days of incubation. Morphologically, *V. fetus* is a motile comma-shaped rod with a single polar flagellum which can be demonstrated by Leifson's flagella stain. Often several or more organisms will form a strand resembling a spirillum.[8] Biochemically, the organism is oxidase positive, catalase positive and does not produce indol. It does not ferment any of the carbohydrates. Serologic identification of the organism is currently being performed at the Communicable Disease Center in Chamblee, Georgia. Problems of isolation and identification of the organism have been discussed by King[1,8] and by Jackson and associates.[10]

Clinical manifestations. The clinical manifestations of *V. fetus* infection in human beings are markedly varied. The infection has been reported in 5 women, 2 newborn babies, and 20 men. The average age of the men was 52 years, and ranged from 31 to 74 years. The most common manifestations are chills, fever, headache, and malaise, with periods of remission and exacerbation. This form of the infection mimics brucellosis. Thrombophlebitis occurs often and may be superficial or deep, may involve any extremity, may be migratory, and may develop at the site of a venipuncture. The infection has a tendency to occur in the debilitated patient with a chronic underlying illness. Apparently any body system may show primary involvement. Infection of the gastrointestinal tract causes diarrhea.[11,12] Infection of the central nervous system may produce a meningitis[8,13-15] or multiple brain abscesses.[4] Jaundice, pneumonia, and septic arthritis have been described.[1,8] The infection responds readily to therapy with the usual doses of tetracycline or chloramphenicol. Penicillin alone, even in massive doses, is usually ineffective.

Endocarditis. *Vibrio fetus* endocarditis has been reported in 3 patients.[1,2] Two patients have been reported on briefly by King[1] in a table in her paper. The first patient was a 50-year-old male painter with an athlete's heart. He had had chills, fever, and an enlarged liver for 2 months. *V. fetus* was cultured from the blood. Treatment and results were not recorded. The second patient was a 47-year-old male janitor with cirrhosis of the liver. He was jaundiced and had a fever. He died of cirrhosis and bleeding. *V. fetus* was cultured from the blood. The case of Auquier and associates[2] has been reported in detail. A 45-year-old male storekeeper developed chills, fever, severe headache, and a transient scarlatiniform eruption 3 days after extraction of a tooth for an apical abscess. On physical examination, the sole abnormal finding was elevation of the temperature. The initial laboratory studies were normal. After 20 days of persistent fever, a diastolic murmur was heard in the third intercostal space to the left of the sternum. Two samples of blood drawn for culturing grew gram-negative motile rods that were not further identified. During the course of illness, a thrombophlebitis developed at the site of a venipuncture. Therapy included in succession penicillin, initially 500,000 units, then 10,000,000 units daily; streptomycin 1 Gm. daily; tetracycline 1.5 Gm. daily;

and erythromycin, 1.2 Gm daily without clinical effect. Finally 31 days after the onset of illness, chloramphenicol 2 Gm daily was administered. This was followed by rapid defervescence and the blood cultures became negative. After the patient had recovered from his illness, the organism isolated from the blood was identified as *V. fetus*. Blood antibody titers to the organism 1 and 2 months after recovery were 1:640 and 1:2500 respectively. The patient on follow up presented the manifestations of aortic insufficiency.

Comments

The predilection of *V. fetus* for involvement of the endothelium of the vascular tree has been remarked upon frequently. To this we may now add that it has a tendency to occupy the aortic valves, particularly when there is a pre-existing valvular deformity. The tendency for the infection to occur in debilitated chronically ill patients is demonstrated again in Case 1. King[1] has suggested that the source of infection in such patients is the testes, for if *V. fetus* is maintained in the testes, as it is in the bull, then when natural body defenses weaken, dissemination may occur. The thrombocytopenia observed in this patient was probably the result of sepsis. However, in the absence of an adequate history, the possibility of a drug induced thrombocytopenia cannot be discarded. The therapeutic response of the second patient to tetracycline is consistent with previous reports. For this reason infection with *V. fetus* should be considered in all cases of bacterial endocarditis, particularly when there is involvement of the aortic valves or when there are peripheral vascular disturbances, such as a mycotic aneurysm or thrombophlebitis.

Summary

The case histories of 2 patients with *Vibrio fetus* endocarditis have been recorded. The organism apparently has a predilection for the aortic valve, particularly when there is a pre-existing abnormality of this valve. Peripheral vascular manifestations such as a mycotic aneurysm or thrombophlebitis, have been observed. The infection responds readily to the usual therapeutic doses of chloramphenicol or tetracycline and does not respond to penicillin alone. *Vibrio fetus*, therefore, should always be considered as a possible cause of bacterial endocarditis.

Addendum

Case 2. It was later learned that several days after this patient's last visit to the clinic he awakened during the night acutely short of breath. A pulmotor squad administered oxygen, but the patient was dead on arrival at a local hospital. Death was attributed to acute pulmonary edema. An autopsy was not performed.

A soluble flagellar antigen was subsequently prepared from the organism that was isolated from this patient. With this we demonstrated precipitin bands in agar gel from three samples of sera obtained 5, 8, and 30 days after the first positive blood culture. These bands were identical to precipitin bands produced from rabbit sera which were immunized with the same organism.

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Rib notching in Marfan's syndrome

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Although rib notching is most commonly associated with coarctation of the aorta, many other causes have been described and extensively reviewed recently.[1-3] Rib notching is usually caused by enlargement of one or more of the main contents of the intercostal space; for example, enlargement of the intercostal arteries will occur in coarctation of the aorta,[4] after the Blalock-Taussig operation,[5] or possibly in pulseless disease;[6] enlargement of the intercostal veins after superior vena caval obstruction;[7] and enlargement of the intercostal nerves in neurofibromatosis.[8] Rib notching may also occur in certain disorders of osseous tissue, including hyperparathyroidism[9] and tuberous sclerosis.[1] Such examples are sometimes referred to as pseudo-rib notching since the upper margin of the rib may also be irregular. Cases have also been described as being due to the pressure of the scapula on the underlying ribs in paralytic poliomyelitis.[11] Whether true rib notching occurs without any associated abnormalities is disputed,[3] but notching restricted to the medial third of the posterior ribs has been described as a normal variant.[3]

Marfan[12] in his original description of the syndrome which bears his name referred to the numerous skeletal abnormalities which may occur. The bony abnormalities usually result from an increase in the longitudinal growth of bone[13] or an increased laxity of tissues and ligaments. The resulting deformities of the chest include pigeon breast, funnel chest, unilateral deformity, and failure of fusion of the sternum, but rib notching does not appear to have been mentioned. Therefore a case is described in which rib notching occurred in Marfan's syndrome and erroneously suggested a diagnosis of coarctation of the aorta.

Case report

A 22-year-old white male shop assistant attended the Mass Miniature Radiography service of his own accord. He was asymptomatic. The 100-mm. film showed some enlargement of the heart, an abnormal aorta, rib notching particularly of the right eighth to tenth ribs, and some deformity of the thoracic cage. A diagnosis of probable coarctation of the aorta was suggested and he was referred to the medical clinic.

On examination, he was tall (77 inches, 195.6 cm.) and thin. The span was 82 inches (208.3 cm.). He had a high arched palate, arachnodactyly, loss of normal cervical curve, and pigeon breast. Apart from myopia, the eyes were normal. He had a collapsing pulse; blood pressure of 120/40 mm. Hg in the left arm, 130/40 in the right arm, and 130/40 in the leg. The femoral pulses were full, equal, and not delayed. Examination of the precordium revealed that the apex beat was in sixth intercostal space in the mid-clavicular line. There was a left ventricular heave. The heart sounds were normal. A loud early diastolic murmur was present down the left sternal edge. No systolic murmurs were audible over either the back or front of the heart. No collaterals were felt over the scapulae. There was no evidence of cardiac failure.

The ECG showed left ventricular hypertrophy and ischemia (S in Lead V + R in Lead V = 41 mm.) with sagging of the S-T segments in the left ven-

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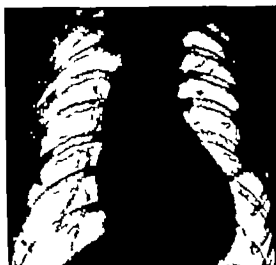


Fig. 1. Chest x-ray film of patient with Marfan syndrome with aortic incompetence showing enlarged left ventricle dilated ascending aorta and aortic arch and moderate rib notching.



Fig. 2. Detail of the sixth and seventh ribs on the right side, showing irregularity of both the upper and lower borders.

tricular leads). The chest x-ray film showed considerable enlargement of the left ventricle a dilated ascending aorta and aortic arch, and moderate notching of the fifth to tenth ribs on both sides (Fig. 1). Detailed examination, however showed irregularity of the upper border of the ribs, particularly the sixth and seventh ribs on the right side (Fig. 2). These changes are similar to those found in the osseous type of pseudo-rib notching. The second and third vertebral bodies showed irregularity of the right border associated with failure of development of their pedicles.

The intravenous pyelogram was normal. The serum calcium was 9 mg. per 100 ml. and the alkaline phosphatase was 7 King-Armstrong units.

Aortography was not recommended in view of the well-known risks of aortic rupture and dissection in Marfan's syndrome.

Discussion

In the patient described here the minifilm showing rib notching enlarged left ventricle, and widened aortic arch was interpreted as suggesting coarctation of the aorta. However clinical examination excluded such a diagnosis and indicated Marfan's syndrome with diffuse dilatation of the thoracic aorta and aortic incompetence. Cardiac abnormalities in Marfan's syndrome were first described by Salle,[14] who reported the case of a 6-week old infant who had an enlarged heart with a patent foramen ovale. It is now generally agreed that dilatation of the aorta which may lead to aortic incompetence dissection or rupture is the most frequent and most important cardiovascular abnormality in Marfan's syndrome.[14]

Although coarctation of the aorta occurs in Marfan's syndrome,[6] Sinclair, Kitchin and Turner[14] after reviewing the literature, have concluded that the association of the two disorders is probably not a direct relationship. Our patient had an increased pulse pressure resulting from aortic incompetence and it has been suggested[7] that an increased pulse pressure in the intercostal arteries may cause rib notching. This is based on the report of Laubry and de Balsac[7] of rib notching in two elderly patients with aortic valve disease and hypertension and in one case of syphilitic aortitis. In view of the relative frequency of aortic incompetence and also hypertension it is remarkable that if they cause rib notching it is not seen more often. Drexler[1] could not recall seeing such a case and Boone and associates[2] reviewed the chest x-ray films of 100 unselected patients who showed generalized atherosclerosis at autopsy. They found only two cases of mild to moderate notching of one and three ribs respectively which they considered to be of the idiopathic variety and they doubt whether an increased pulse

pressure can cause notching. No report of aortic incompetence causing rib notching in a young person could be traced. In this case it is considered that the rib notching was related to the skeletal abnormalities of Marfan's syndrome which resulted in an irregularity of both the upper and lower surfaces of the ribs.

Summary

A case of Marfan's syndrome with rib notching is described. Although the patient had aortic incompetence and aortic dilatation, it is considered that the rib notching was related to the skeletal abnormalities.

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Pulmonary arteriovenous fistula and rheumatic cardiac disease

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The occurrence of peripheral cyanosis (normal arterial oxygen saturation) in patients with severe acquired cardiac valvular disease is not uncommon. However, the occurrence of central cyanosis (reduced arterial oxygen saturation) in these patients is distinctly unusual and suggests the presence of a right-to-left (venoarterial) shunt or extreme pulmonary disease. A patient with severe rheumatic valvular disease was noted to have generalized cyanosis and was found to have a pulmonary arteriovenous fistula. A review of published reports of pulmonary A-V fistulas revealed only 2 other patients with coexistent cardiac valvular disease,[1,2] and consequently prompted this report.

Case report

M. P. (#05-45-49), a 50-year-old white woman who had had acute rheumatic fever during late childhood, was told during her twenties that she had a "heart murmur." She was asymptomatic until age 47, when exertional dyspnea appeared. Thereafter symptoms of cardiac decompensation rapidly progressed despite digitalization and diuretic therapy and, in the 6 months before admission, she became markedly incapacitated, bedridden, and cachectic (35 kilograms).

On admission, she was dyspneic and tachypneic (42 per minute) while sitting up in bed. Her lips and nail beds were cyanotic but there was no digital clubbing or cutaneous or mucosal telangiectasia. The blood pressure was 100/70 mm. Hg and the heart was enlarged. A Grade 3/6 pansystolic blowing murmur and a Grade 3/6 diastolic rumble were audible over the cardiac apex. A grade 4/6 high-pitched decrescendo diastolic blowing murmur was heard at the lower left sternal border. No murmur was heard over the back. The liver was enlarged, but there was no peripheral edema.

The hematocrit was 46 per cent, and the hemoglobin was 14.3 Gm. per cent. Chest roentgenograms (Fig. 1) showed a mass, 6-by-3 cm. in size, in the left lower lung field, cardiomegaly, and calcium in the region of the mitral valve. The electrocardiogram revealed atrial fibrillation, right axis deviation, and right ventricular hypertrophy. Femoral arterial hemoglobin oxygen saturation was 76 per cent while the patient was breathing room air and rose to 84 per cent after the patient breathed 100 per cent oxygen for 10 minutes. Before cardiac catheterization studies and angiocardiography could be performed, the patient developed acute pneumonia and died.

At autopsy (A64-127) the mitral valve was rigid and calcified and showed evidence of being both insufficient and stenotic (Fig. 2). The aortic valve leaflets were thickened and slightly retracted. The left atrial appendage contained old and recent thrombus. In the lingular portion of the left upper lobe, immediately posterolateral to the heart, there

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Fig. 1. Chest roentgenograms. Posteroanterior view (left), lateral view (middle) and anteroposterior tomogram (right). The pulmonary A-V fistula is designated by the arrows.



Fig. 2. Photograph of the left atrium (L.A.), mitral valve, and the left ventricle (L.V.). The insert shows the unopened diseased mitral valve as seen from the left atrium.

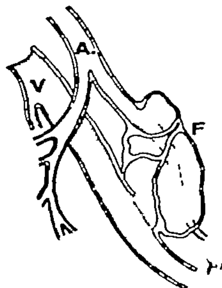


Fig. 3. Diagram of the pulmonary A-V fistula. A, Pulmonary artery. V, Pulmonary vein. F, Pulmonary A-V fistula. The diameter of the pulmonary vein is greater than that of the pulmonary artery.

was saccular pulmonary A-V fistula (Figs. 3 and 4). Histologic sections of the lungs showed no changes indicative of hypertensive pulmonary vascular disease.

Discussion

The majority of patients with pulmonary A-V fistula have central cyanosis, digital clubbing, polycythemia and a localized continuous murmur over the chest. The present patient, however, like 2 previously reported patients with coexistent cardiac valvular disease and pulmonary A-V fistula,[2] did not have clubbed digits, polycythemia, or a thoracic murmur which could be definitely attributed to a shunt through the fistula. Although occasionally an individual with a pulmonary

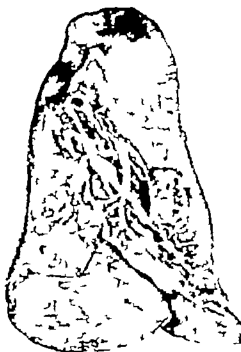




Fig. 4. Photograph of the pulmonary A-V fistula in the lingular portion of the left upper lobe. *Left.* The fistula is shown before removal of its medial wall. *Right.* Close-up view showing the quadrilocular fistula.

A-V fistula has no detectable thoracic murmur,[3] it is more likely that in the present patient a murmur was produced by the shunt but was masked by the cardiac murmurs.

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Review

The nature and prevention of prosthetic valve endocarditis

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Prosthetic valve infection represents a dangerous complication of prosthetic heart valve surgery This type of surgery has afforded the unique experience of studying bacterial endocarditis† from its inception This study embraces some aspects of the prevention, diagnosis, and treatment of infection on prosthetic valve sites Our experience has been examined and the literature has been reviewed

Material and methods

The records of 288 consecutive patients who underwent prosthetic ball valve implacement at the Peter Bent Brigham and Mount Auburn Hospitals have been reviewed There were 162 aortic valve replacements, 105 mitral valve replacements, and 21 double valve replacements. In 218 patients, blood cultures were obtained only when prosthetic valve infection was suspected In 70 patients blood cultures were obtained routinely during the first week after operation. Two hundred and forty three patients received no specific antistaphylococcal prophylaxis (methicillin) after operation. Forty five patients received various regimens of prophylactic methicillin and oxacillin Thirty five patients of the entire group of 288 patients (12 per cent) had one or more positive blood cultures in association with fever Twenty-eight of these patients received no methicillin prophylaxis, whereas 7 of these patients received various regimens of methicillin prophylaxis.

The 35 patients with positive blood cultures were divided into three groups *Group I* those with essentially proved infection in the region of the prosthetic valve *Group II* those with probable infection in the region of the prosthetic valve and *Group III* those with questionable infection in the region of the prosthetic valve

Group I

Group I consisted of 10 patients in all of whom there was *autopsy evidence of bacterial endocarditis* in the region of the prosthetic valve (Table I)

Patients 1 3 had either purulent material

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†The term "bacterial endocarditis," when applied to patients with prosthetic heart valves refers to infection in relation to the prosthetic valve

Table I Group I Autopsy evidence of bacterial or mycotic endocarditis

Patient	Blood culture*	Postmortem culture	Purulent material	Vegetations		Suture disruption
				Site	Microscopic	
1	Staph. albus (3)	Not done	Valve ring (bacteria on microscopic)	None		+ (Valve sloughed)
2	Staph. aureus coag + (7)	Contaminants	Valve ring	None		+
3	Staph. aureus coag + (2) Staph. aureus coag neg (1) Pseudomonas (1) Proteus (1)	Not done	Suture channel (microscopic only)	?		0
4	A. faecalis (10) Diphteroids (1)	A. faecalis	0	Valve ring	Bacteria	0
5	Staph. aureus coag + (1)	Staph. aureus coag +	0	Valve ring	Not done	0
6.	Staph. aureus coag + (5) Paracolobactrum aerogenes (6)	Candida albicans A. aerogenes	0	Struts and valve ring	Candida in vegetation	0
7	Staph. aureus coag + (4)	Staph. aureus coag +	0	Valve ring	Not done	0
8	Beta hemolytic streptococcus (1)	0	0	Valve ring	No bacteria	0
9	Staph. aureus coag neg (2)	Staph. aureus coag neg	0	None		0
10	Staph. aureus coag + (1) Aspergillus (1)	Staph. aureus coag +	0	None		+

*Number in parentheses indicates number of positive blood cultures.

on gross examination or colonies of bacteria on microscopic examination in the region of the valve ring or suture channels. These patients, therefore, represent instances of proved bacterial endocarditis.

Patients 4-7 had vegetations on the prosthetic valve ring or upon the struts of the valve. Postmortem cultures from the region of the vegetations revealed bacteria that were identical or culturally similar (Patient 6) to those that were found in blood cultures during life. These cases satisfy Gross and Friedberg's criteria for postmortem evidence of bacterial endocarditis.[1]

Patients 8-10 revealed less definitive postmortem evidence of prosthetic valve infection and therefore will be discussed in more detail. Patient 8 suffered a shaking chill associated with a temperature of 102°F one day after operation. A sample of blood for culturing was drawn and penicillin was given immediately afterward. The patient died 3 days later from multiple cerebral emboli. Vegetations were found at autopsy, but culture and Gram stains of the vegetations were negative, probably because of sterilization by the penicillin.[8]

Patient 9 suffered a low-grade fever for 2 weeks after operation. Two blood cultures revealed coagulase negative staphylococci. The temperature was abating after methicillin and penicillin therapy when the patient died from intracerebral hemorrhage secondary to hypoprothrombinemia. Postmortem culture of blood from the region of the aortic prosthesis, obtained within 15

hours after death also revealed coagulase-negative staphylococci. There was no gross or microscopic evidence of infection.

Patient 10 was rehospitalized because of fever and petechiae. Blood culture revealed coagulase-positive staphylococci. Sudden death occurred 1 day later. Autopsy performed within 15 hours after death revealed a thrombus partially occluding the prosthetic outflow tract. Culture of the thrombus revealed coagulase-positive staphylococci. The accuracy of postmortem blood cultures obtained within this period of time has recently been emphasized.[3] There was no gross evidence of infection. Although free aortic insufficiency due to suture separation was present, microscopic sections along the suture lines were not reported.

Patients 8 through 10 very probably represented cases of bacterial endocarditis. Death in each patient in Group I, with the exception of Patient 9, was related at least in part to bacterial endocarditis situated in the region of the prosthetic valve.

Only 1 patient in Group I received methicillin prophylaxis (Patient 9). Five patients in this group received no antibiotic prophylaxis and 4 patients received various regimens of penicillin, streptomycin, tetracycline, or novobiocin (Table II).

Group II

Group II consisted of 7 patients, all of whom had *probable bacterial endocarditis* on the basis of two or more blood cultures that were positive for the same organism. Six of the patients survived after massive antibiotic therapy. One patient (Patient 14) died, but no evidence of infection was discovered at autopsy (Table II). This patient had been rehospitalized because of congestive heart failure and recurrent pulmonary emboli 6 weeks after mitral and aortic double valve implacement. Ligation of the inferior vena cava was performed and was complicated by cardiac arrest. Later, pneumothorax occurred. Ten days after ligation of the inferior vena cava, the temperature rose to 102.6°F. Two cultures of venous blood and culture of the left brachial arterial cannula revealed coagulase-positive *Staphylococcus aureus*. Methicillin, chloramphenicol, and penicillin were given. However, mental status gradually deteriorated, and neurologic signs of intracerebral lesions developed. One month after ligation of the inferior vena cava, the patient died. Autopsy revealed no evidence of bacterial endocarditis. Presumably, the endocarditis had been cured by therapy. Thrombi were found on the aprons of both the mitral and aortic prostheses, as well as proximal to the site of ligation of the inferior vena cava. Cerebral and pulmonary infarctions were present.

Group III

Group III consisted of 18 patients, all of whom had only *one positive blood culture. All but one survived. In the patient who died no evidence of bacterial endocarditis was discovered at autopsy.* All patients in this group were febrile at the time of the positive blood culture, and 9 patients had in association with the positive blood culture infections elsewhere, pleural effusions, or a history of additional surgery after valve implantation (Table II).

Blood cultures in the first 12 patients of Group III were obtained because of the suspicion of bacterial endocarditis. Blood cultures in the other 6 patients were obtained as part of the routine postoperative laboratory tests. Two patients in Group III had false-positive blood cultures on the basis of becoming well without antibiotic therapy. All others received therapeutic doses of antibiotics at the time of the positive blood culture, or shortly thereafter, even though the diagnosis of bacterial endocarditis rarely was made in these patients.

Results

The 43 bacteria or fungi cultured from the blood in the 35 patients in this study are listed in Table III. Twenty-three of the entire group of 35 patients were infected with staphylococci (66 per cent). Thirteen of the 17 patients who comprised Groups I and II were infected with staphylococci (76 per cent). Thus, where the evidence was strongest, the organism was staphylococcus. Some of these patients were infected with other organisms in addition to staphylococci. Patient 6 had a proved mixed infection due to *Staphylococcus aureus*, *Paracolobactrum aerogenes*

Table II

Patient	*Valve*	*Organism*	*Number of positive blood culture*	*Lived died*	*Suture material*	*Onset of fever (days postop)*	*Time of first positive blood culture (days postop)*	*Interval between fever and therapy (days)*	*Prosthetic regurgitant murmur*	*Severity of illness* (1+ to 4+)*	*Cerebral emboli*	*Rectal temp (°F)*
Group I												
1	A	Staph albus	3	D	Silk	21	35	90§	+	1+		101
2	A	Staph aureus coag +	7	D	Silk	24	28	21	0	1+	0	102
3	A	Staph. aureus coag +	2	D	Silk	1	3	7	0	3+	0	104
		Staph aureus coag neg	1									
		Pseudomonas	1									
		Proteus	1									
4	A	A faecalis	10	D	Silk	21	49	3	0	1+	+	104
5	A	Staph aureus coag +	1	D	Tev	1	21	21	0	4+	0	105
6	M	Staph aureus coag +	5	D	Silk	1	42	3‖	0	3+	0	104
		Paracolobactrum aerogenes	6									
		Candida albicans (autopsy)										
7	A	Staph. aureus coag +	4	D	Gut	1	2	3	0	1+‡	0	103
8	M	Beta strep	1	D	Dek	1	1	1	0	1+‡	+	102
9	A	Staph aureus coag neg	2	D	Tev	1	14	1	0	1+	0	101 8
10	A	Staph aureus coag +	1	D	Tev	70	70	No Rx	+	2+	+	101 8
		Aspergillus	1									
Group II												
11	A	Staph. aureus coag +	2†	L	Tev	3	17	1	0	2+	+	102 8
12	A	Staph aureus coag neg	3	L	Tev	2	10	1	0	2+	0	101
13	M	Herrellea	2	L	Tev	1	1	1	0	1+‡	0	101 2
14	M & A	Staph. aureus coag +	2	D	Silk	70	70	1	+	4+	+	102 6
15	M	Staph. aureus coag +	3	L	Tev	21	28	12	+	1+	0	100 6
16	A	E. coli	4	L	Silk	21	24	7	0	1+	+	102
17	M	Staph. aureus coag +	5	L	Tev	10	38	28	0	3+	+	105

*At time of first positive blood culture.
**Received methicillin 4 to 7 days after operation.
***Received methicillin followed by oxacillin, for 10 days or more.
†One preoperatively and one postoperatively.
‡Early postoperatively.
§Previous suboptimal therapy.
‖Therapy intermittent.
Tev: Tevdek. *Dek*: Deknatel. *Gut*: Catgut. *Chlor*: Chloramphenicol. *Colisti*: Colistimethate. *Eryth*: Erythromycin. *Kan*: Kanamycin.

WBC (thousands)*	Splenomegaly or petechiae*	Urine RBC: If first positive blood culture	Urine RBC: Later	Antibiotic prophylaxis after surgery	Treatment	Associated circumstances
?	0	?		Pen Strep	Meth	None
10–14	0	0	2–3	Tetra	Pen, Novo	Valve biopsy "SBE" ctive
?	0	?	?	None	Chlo, Kan	Tracheitis, Staph. coag ? Proteus, Pseudomonas
8	0	0–1	?	Novo	Chlo, Oxa Colisti	Valve contamination gram + bacilli
22	0	?	1–3	Pen	None	Wound, Staph. aureus coag +
?	0	?	0–1	None	Meth Chlo, Eryth	Pneumonia, Staph coag + A. aerogenes, Candida albicans
7 9	0	0	?	None	Chlo, Eryth	None
?	0	?	?	None	Pen	None
7–12	0	0–1	?	Meth, Oxa***	Meth	Wound infection Staph. aureus coag +
8–19	P	1 2	?	None	None	Urine, Staph. aureus coag +
18 9	0	5–10	?	Meth, Oxa**	Meth, Oxa Tetra	Staph. aureus coag + (preop. blood culture)
12 5	0	?	30–60	Meth Oxa***	Meth, Pen Strep, Chlo	Sputum and wound, Staph aureus coag neg
?	0	?	?	Meth,	Meth, Pen Strep Chlo, Eryth	None
10	0	4–6	?	Pen, Strep	Meth	IVC ligation (no prophylaxis) Arterial cannula, Staph aureus coag +
10–12	0	6–7	21 22	Pen	Cephalothin	Wound, Staph aureus coag neg and coag +
16 5	0	0	2 3	None	Chlo Eryth	Urine E coli
?	0	?	30–40	Pen Strep	Meth	Staph. albus wound

Meth Methicillin. *Novo* Novobiocin. *Oxa* Oxacillin. *Pen* Penicillin. *Strep* Streptomycin. *Tetra* Tetracycline. *N Rx* No therapy

Table II—Cont d

Patient	*Valve*	*Organism*	*Number of positive blood cultures*	*Lived or died*	*Suture material*	*Onset of fever (days postop.)*	*Time of first positive blood culture (days postop.)*	*Interval between fever and therapy (days)*	*Prosthetic regurgitant murmur*	*Severity of illness (1+ to 4+)*	*Cerebral emboli*	*Rectal temp. (°F)*
Group III												
18	A	Staph aureu coag +	1	L	Silk	5	3	4	+	1+	0	103
19	A	Staph aureu coag +	1	L	Tev	1	7	1	0	1+	0	102 4
20	A	Alpha strep	1	L	Silk	1	10	5	0	1+	0	101 6
21	A	Alpha trep	1	L	Tev	14	14	1	0	1+	0	102
22	M	Staph ureus coag neg	1	L	Tev	14	42	5	+	3+	0	100 2
23	A	Staph ureus coag +	1	L	Tev	1	4	No Rx	+	1+†	0	101
		Diphtheroids	1									
24	A	Staph. aureu coag neg	1	L	Tev	3	6	1	0	2+	+	102
25	M	Diphtheroids	1	D	Silk	1	1	1	0	1+†	0	102
26	M + A	Staph. ureus coag +	1	L	Silk	2	2	1	M	1+†	0	103 6
27	M	Staph. aureus coag neg	1	L	Silk	1	14	14	0	1+	0	102 6
28	A	Alpha strep.	1	L	Silk	42	46	10	0	1+	0	101
29	M	Staph aureus coag +	1	L	Tev	14	14	1	0	2+	0	101 2
30	M	Gamma strep.	1	L	Silk	1	1	1	0	1+†	0	100 8
31	M	Achromobacter	1	L	Tev	1	3	4	0	1+†	0	103
32	A	Staph. aureus coag neg	1	L	Silk	1	1	1	0	1+†	0	101
33	M	A. faecalis	1	L	Silk	1	1	1	0	1+†	0	101
34	M	Herrellea	1	L	Silk	2	1	1	0	1+†	0	101
35	A	Aerobacter	1	L	Silk	14	14	No Rx	0	1+	0	100 6

*At time of first positive blood culture.
**Received antibiotics 4 to 7 days after operation.
†Early postoperatively.
‡Three days only.

and *Candida albicans*. Bacterial endocarditis due to coagulase-negative staphylococci also occurred (Patients 9 and 12).

In 5 of the 23 patients infected with staphylococci, organisms cultured from the blood revealed a coagulase or chromogen-producing characteristic different from that of the staphylococcus found in the associated infection. Patient 3, with proved bacterial endocarditis, had blood cultures for both *Staphylococcus aureus* coagulase positive and *Staphylococcus aureus* coagulase negative (Table I).

The chance that a particular blood culture is falsely positive is not more than 2 per cent, on the basis of the fact that there were 6 positive blood cultures out of 300 blood cultures obtained routinely in 63 patients not suspected of having endocarditis.

Factors predisposing to bacterial endocarditis in the 17 patients in Groups I and

W BC (thousands)	Splenomegaly or petechiae*	Urine RBC: At first positive blood culture	Urine RBC: Later	Antibiotic prophylaxis after surgery	Treatment	Associated circumstances
11 7	0	?	2–3	None	Meth	Wound, Staph. aureus coag + (pparent later)
21	P	15–20	?	Pen, Strep, Chlo, Eryth	Meth	Stool, Staph. aureus coag +
8 6	0	?	?	Pen	Pen	None
9 6–12	0	2–3	?	Pen	Chlo Eryth	History "SBE
12 9	0	5–6	?	Pen	Meth	Wound Staph. aureus coag.+
8	0	0	?	Pen Strep‡	None	None
12 5	0	20–30	?	Pen, Strep	Chlo, Eryth	Sputum Staph aureus, coag Urine Staph. aureus coag +
?	0	50	?	Pen	Pen	None
6	0	?	2–3	None	Pen Chlo	None
9–13	0	0–1	?	None	Chlo, Eryth	Pleural effusion Culture
9	P	0	?	Tetra	Pen	IVC ligation
6 3	0	0	?	Meth**	Meth	Draining wound Culture
8 8	0	?	?	Pen	Pen	None
?	0	?	?	None	Pen, Chlo	None
?	0	?	?	None	Pen, Strep, Meth	Tracheitis (apparent later)
?	0	?	3–4	Pen Strep, Novo	Novo, Pen Strep	None
?	0	?	?	Pen, Strep, Meth**	Pen Strep Meth	None
10 3	0	?	?	Strep Novo	None	None

II were wound infection in 5 patients, proved surgical contamination or preceding subacute bacterial endocarditis in 3 infection of the respiratory tract in 2 and infection of the urinary tract in 2 (Table IV) An infected indwelling arterial cannula may have led to bacterial endocarditis in 1 patient. In 4 patients there was no apparent predisposing incident. Surgical contamination is assumed to have occurred in these 4 patients.

The history most suggestive of bacterial endocarditis was fever in the early postoperative period (first 4 weeks) especially if associated with evident infection or fever in the late postoperative period after an infection or surgical procedure Fifteen of the 17 patients in Groups I and II who had bacterial endocarditis developed fever during or before the fourth postoperative week and 14 before the third postoperative week (Table V) Fever occurred in the

Table II—Cont'd

Patient	Valve	Organism	Number of positive blood cultures	Lived or died	Suture material	Onset of fever (days postop.)	Time of first positive blood culture (days postop.)	Interval between fever and therapy (days)	Prosthetic regurgitant murmur	Severity of illness (1+ to 4+)	Cerebral emboli	Rectal temp. (°F)
Group III												
18.	A	Staph. aureus coag. +	1	L	Silk	5	5	4	+	1+	0	103
19	A	Staph. aureus coag. +	1	L	Tev	1	7	1	0	1+	0	102.4
20	A	Alpha strep.	1	L	Silk	1	10	5	0	1+	0	101.6
21	A	Alpha strep.	1	L	Tev	14	14	1	0	1+	0	102
22	M	Staph. aureus coag. neg.	1	L	Tev	14	42	5	+	3+	0	100.2
23	A	Staph. aureus coag. +	1	L	Tev	1	4	No Rx	+	1+†	0	101
		Diphtheroids	1									
24	A	Staph. aureus coag. neg.	1	L	Tev	3	6	1	0	2+	+	102
25	M	Diphtheroids	1	D	Silk	1	1	1	0	1+†	0	102
26	M + A	Staph. aureus coag. +	1	L	Silk	2	2	1	M	1+†	0	103.6
27	M	Staph. aureus coag. neg.	1	L	Silk	1	14	14	0	1+	0	102.6
28	A	Alpha strep.	1	L	Silk	42	46	10	0	1+	0	101
29	M	Staph. aureus coag. +	1	L	Tev	14	14	1	0	2+	0	101.2
30.	M	Gamma strep.	1	L	Silk	1	1	1	0	1+†	0	100.8
31	M	Achromobacter	1	L	Tev	1	3	4	0	1+†	0	103
32	A	Staph. aureus coag. neg.	1	L	Silk	1	1	1	0	1+†	0	101
33	M	A. faecalis	1	L	Silk	1	1	1	0	1+†	0	101
34	M	Herrellea	1	L	Silk	2	1	1	0	1+†	0	101
35.	A	Aerobacter	1	L	Silk	14	14	No Rx	0	1+	0	100.6

At time of first positive blood culture.
**Received methicillin 4 to 7 days after operation.
†Early postoperatively.
‡Three days only.

and *Candida albicans*. Bacterial endocarditis due to coagulase-negative staphylococci also occurred (Patients 9 and 12).

In 5 of the 23 patients infected with staphylococci, organisms cultured from the blood revealed a coagulase or chromogen-producing characteristic different from that of the staphylococcus found in the associated infection. Patient 3, with proved bacterial endocarditis, had blood cultures for both *Staphylococcus aureus* coagulase positive and *Staphylococcus aureus* coagulase negative (Table I).

The chance that a particular blood culture is falsely positive is not more than 2 per cent on the basis of the fact that there were 6 positive blood cultures out of 300 blood cultures obtained routinely in 63 patients not suspected of having endocarditis.

Factors predisposing to bacterial endocarditis in the 17 patients in Groups I and

Table IV. Associated incidents predisposing to bacterial endocarditis (Groups I and II)

Incident	Number of patients
Wound infection	5*
Urinary tract infection	2
Respiratory tract infection	2
Ivalon sponge contamination	1
Valve biopsy at surgery—SBE	1
Preop. blood culture positive	1
Inferior vena cava ligation	1†
Indwelling arterial cannula contamination	1†
No obvious cause	4

*One wound infection became apparent a few days after the first positive blood culture.
†Same patient.

Table V. History suggestive of bacterial endocarditis (Groups I and II)

Fever before fourth postop. week	15 of 17
(During third postop. week—11 of 17)	
Associated or preceding infection	13 of 17
Late postop. fever after another surgical procedure	1 of 17

Table VI. Signs of bacterial endocarditis at time of first positive blood culture (Groups I and II)

Clinical signs	Number of patients
Look well	9/17
Temperature (rectal) less than 102°F	5/16
White blood cell count of 10,000 or less	3/11
Red blood cells in urine (1 to 2 or more per high-power field)	4/9
Insufficiency murmur	4/17
Cerebral emboli	7/16
Petechiae	1/17
Spleen palpable	0/17
Splinter hemorrhages	0/17
Osler's nodes	0/17
Hematocrit less than 31 per cent	0/17

*The lower number indicates the number of patients in Groups I and II about whom the indicated information could be obtained at the time of the first positive blood culture.

(63 per cent) and 2 of 7 with wettable sutures survived (29 per cent).* An approximately equal distribution of non-wettable and wettable sutures was present in Group III (patients with single positive blood cultures).

Localization of the endocarditis is summarized in Table IX. The vegetations in all cases were located at the base of the prosthetic valve. In 1 patient the vegetations also extended along the struts. Purulent material was located at the suture sites in 2 patients with silk sutures and in 1 patient with Tevdek sutures. (The silk sutures were broken in Patient 7. Autopsy reports did not indicate clearly whether disruption of the sutures in Patients 1 and 10 was due to destruction of tissue or destruction of suture material, but presumably it was the former.)

The prosthetic valve seat and/or sutures was the site of post-valve-implacement endocarditis in all (8) autopsied cases reported by others.[1-4]

Discussion

Bacterial endocarditis is an important complication of valve replacement. Thirty-five of 288 (12 per cent) patients at the Peter Bent Brigham and Mt. Auburn Hospitals who underwent valve replacement developed septicemia, as defined by positive blood cultures in the presence of fever. The deaths of 9 of 243 patients (3.7 per cent) who were operated upon before antistaphylococcal prophylaxis was used were due in part to prosthetic valve infection.

Infection upon prosthetic heart valves is a problem at all surgical centers. Before routine antistaphylococcal prophylaxis was used, the incidence of fatal bacterial endocarditis associated with ball valve prostheses, as gleaned from the literature,[14] was 13 of 417 cases or 3.1 per cent (Fig. 1). This is similar to the experience at this hospital.

Factors that would lead one to expect a high incidence of infection upon prosthetic valves, especially in the early postimplacement period, are trauma,[15,16] foreign body,[17] focus of infection in sutures,[8]

*Chi-square technique yields a p value of approximately 0.4, indicating no statistical significance.

Table VII Relationship of survival to treatment delay

	Time interval between onset of fever and antibiotic therapy		
	1 7 days	8 14 days	3 weeks or more
Group I (endocarditis—died	5	0	3
Group II (or more pos tive blood c ltures—cured)	5	1	1
Group III† ingle pos tive blood culture—cured)	14	2	0

Patient 9 was excluded because death was unrelated endocarditis Patient 10 was excluded because the temperature before readmission was established

Two patients were excluded because they were not treated

Table VIII Relationship of survival to intracardiac suture material

Suture material	Group I (Proved endocarditis—died)	Group II (More than one positive blood culture—cured)	Group III (One positive blood culture only—cured)
Nonwettable (Tevdek Dekmatel)	3	5	7
Wettable (silk)	5	2	11
Absorbable (Gut	1		

*Patient No. 9 in Group I died of causes completely unrelated to infection and is excluded from this table.

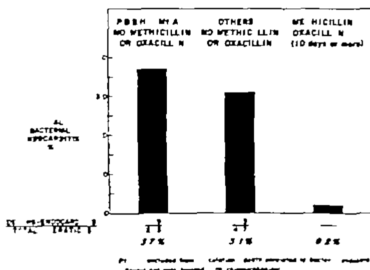


Fig. 1 Relationship of methicillin-oxacillin prophylaxis to the incidence of f tal bacterial (or mycotic) endocarditis in patients with ball valve prostheses Without methicillin or oxacillin prophylaxis, over 3 per cent of all patients operated upon died of bacterial (or mycotic) endocarditi With appropriate prophylaxis fatal bacterial endocarditis was virtually eliminated.

Table IX. Group I. Cardiac findings at autopsy

Finding	Number of patients
Vegetations	5 of 10
Valve base	4
Struts	1
Purulent material (gross or microscopic)	3 of 10
Sutures	
Valve base	1
Sutures out	3 of 10
Silk	2
Teflon	1

and white blood cell dysfunction after extracorporeal circulation.[18] Late infection is less of a problem because in the normal healing process, the sewing ring is quickly covered by a pseudoendothelium that becomes an effective barrier to bacterial implantation.[12] Mechanical trauma to valves makes them susceptible to bacterial endocarditis as was shown by Rosenbach[15] and Powers.[16] In 1942 Harken[17] demonstrated the vulnerability of intracardiac foreign body sites to bacterial endocarditis. In 1957 Bahnson[18] demonstrated that suture material may harbor foci of infection. Removal of infected silk sutures resulted in the cure of 5 patients who had refractory bacterial endocarditis after surgical repair of congenital defects. In 4 of 5 patients, cultures of the sutures grew bacteria. Impaired phagocytosis by white blood cells was demonstrated by Unger[19] in 1963. In spite of a normal white blood count, phagocytosis may be impaired for as long as 18 days after extracorporeal circulation.

The fact that each of these factors may be important is indicated by a serial increase in the fatal bacterial (or mycotic) endocarditis that occurs more commonly after prosthetic valve replacement than in other heart surgery and more commonly in open-heart surgery[20,21] than in closed heart surgery[22,23] (Fig. 2). There is a 3.1 to 3.7 per cent mortality from bacterial (or mycotic) endocarditis in patients not treated prophylactically with methicillin after ball valve replacement, a 0.9 per cent mortality in patients presumably not treated with methicillin after other types of open heart surgery,[20,21] and a 0.6 per cent mortality from bacterial endocarditis in patients also not receiving methicillin after closed mitral or aortic valvuloplasty.[22,23]

Prophylactic antistaphylococcal antibi

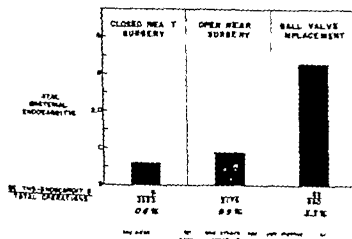


Fig. 2. Comparison of the incidence of fatal bacterial (or mycotic) endocarditis after various types of heart surgery in patients not given methicillin or oxacillin prophylaxis. The incidence of fatal bacterial endocarditis is greater after open-heart surgery than after closed-heart surgery, and greater after ball valve implacement than after other types of open-heart surgery.

otics, if given long enough and in adequate dosage, can nearly eliminate staphylococcal endocarditis. Six hundred and nineteen patients were given prophylactic methicillin 4 to 8 Gm daily until oral medication could be given at which time oxacillin 2 Gm daily was given for a total of *at least* 10 days.[8,13] Many of the patients were given oxacillin for as long as 3 months after valve implantation.[34] Allergic patients were given chloramphenicol.[34] There was only 1 fatal infection among this group of 619 patients a fatal case of Pseudomonas septicemia after a wound infection. One additional patient developed nonfatal staphylococcal septicemia after a postoperative cardiac catheterization. He did not receive prophylactic antistaphylococcal drugs at that time. Therefore, *the incidence of fatal bacterial endocarditis in patients treated prophylactically* was 0.2 per cent* a dramatic decrease from the 3.7 per cent mortality due to endocarditis in those not treated prophylactically (Fig. 1).

Prophylactic treatment for less than 10 days may be of no value. Two hundred and five patients at the Mayo Clinic were treated prophylactically with methicillin for at least five days after operation.[28,33] There was 1 death due to bacterial endocarditis during hospital convalescence and 6 late deaths at least 5 of which showed evidence of bacterial endocarditis in the first 4 months after valve implantation.[28] The incidence of fatal endocarditis in this group was 3.4 per cent, approximately the same incidence as that in patients not receiving prophylactic methicillin.

If localized infection occurs, more vigorous antibiotic administration is appropriate in order to prevent bacterial endocarditis. At the Peter Bent Brigham and Mt. Auburn Hospitals, 45 patients received methicillin followed by oxacillin for 4 days or more after valve implantation. Although there were no deaths attributed to bacterial endocarditis in this group 6 patients did develop positive blood cultures 4 of which were due to staphylococcus. Each of the patients with staphylococcal septicemia had some apparent preceding cause that may have led to bacterial endocarditis, such as wound infection or preoperative bacteremia. Methicillin followed by 2 Gm daily of oxacillin even when continued for 10 days or more, seems to have been inadequate to prevent bacterial endocarditis under these conditions.

Staphylococcus is the organism most frequently cultured from the blood after prosthetic valve surgery. Staphylococcus was the offender in 13 of 17 patients with proved septicemia in this study and in 18 of 26 patients reported in the literature.[4-6,11-13,27] Of 95 patients with septicemia associated with heart surgery other than prosthetic valve implacement who were reported in the literature, 67 were infected with staphylococci (Table X).[22,23,29-38] Therefore the incidence of staphylococci as a cause of septicemia in patients who underwent all types of heart surgery as accumulated from many reports was 71 per cent.[4,6,11,13,22,23,27-38] In nonprosthetic valve heart surgery coagulase-negative *Staphylococcus aureus* was reported as frequently as coagulase-positive *Staphylococcus aureus* as a cause of septicemia.[22,23,31-36]

Four patients in Group II of this study who had unquestioned septicemia due to staphylococcus survived indicating that staphylococcal septicemia in patients with prosthetic valves is not uniformly fatal. (The prostheses in each of these patients were sutured with nonwettable material.) In series reported by others, at least 2 cases of staphylococcal septicemia in patients with ball valve prostheses have been cured by medical means.[7,8] Once the patients who have had heart surgery (but not open heart surgery) became infected the mortality from septicemia has been about 41 per cent (29 out of 70 cases).[22,23,31] The mortality rate from *staphylococcal* septicemia after closed heart surgery has been somewhat higher at 46 per cent (12 of 26 cases).[22]

In 6 patients (Patients 3, 9, 15, 17, 22 and 24) 4 with proved sepsis the staphylococci found in the blood had coagulase or pigment-producing characteristics that were different from the coagulase or pigment producing characteristics of the staphylococci cultured from the associated wound or infection of the respiratory tract. Coagulase and pigment production are subject to frequent variations.[39] Further

*Prophylactic treatment consisted of methicillin, 4 to 8 Gm. daily intravenously followed by oxacillin, 2 Gm. daily for total of at least 10 days.

Table V. Relative incidence of staphylococcal endocarditis

	*Ball valve prostheses**	*Nonprosthetic heart valve surgery*	*Total*
Staphylococcus†	31	67‡	98
Streptococcus	2	14	16
Others†	10	14	24
A. faecalis			
Paracolobactrum			
Proteus			
Candida albicans			
Aspergillus§			
Herrellea			
Escherichia coli			
Flavobacterium			
Pseudomonas			
Aerobacter			
Nocardia asteroides‖			
Cryptococcus‖			

*Includes Groups I and II and reports from the literature that described both fatal and nonfatal cases.
†Some patients had positive blood cultures for more than one organism.
‡Includes 30 coagulase +, 33 coagulase −, and 4 coagulase ?
§Proved late death in drug addict (Reference 6).
‖Reference 8.

more the routine testing for these characteristics is subject to technical difficulties.[9] Neither of these characteristics should be relied upon absolutely for taxonomic purposes.[11] It is emphasized that a blood culture should not be discounted as a contaminant because the coagulase determination or pigment production of the staphylococci differ from the characteristics of the staphylococci cultured from other sites.

The histories offered some clues to the early diagnosis of septicemia. Circumstances most often associated with septicemia were (1) fever occurring before the fourth postoperative week, usually but not always, associated with evident infection in wounds, lungs, or elsewhere; (2) fever in the late postoperative period almost always associated with infection in wounds, lungs, or elsewhere, or after a surgical manipulation (Tables IV and V). Similar circumstances were observed by others,[1,12] although cases of late infection have occurred without apparent predisposing events.[12] The onset of fever occurred in the early postoperative period or followed an infection or other precipitating circumstance in the late postoperative period.* The mild febrile reaction that occurs after cardiotomy with extracorporeal circulation usually disappears by the fifth or sixth day after operation, whereas fever due to septicemia of course persists.[13]

Signs of illness are nonspecific and the diagnosis is difficult to make on the basis of clinical evidence. Possible clues to the diagnosis of bacterial endocarditis are indicated by the presence of a murmur of prosthetic insufficiency, signs of cerebral emboli, and microscopic hematuria (Table VI).

The presence of even one or two red cells per high-power field is a deviation from that which is usually seen during the convalescent period. Postperfusion hematuria almost invariably disappears by the second postoperative week. Ninety-nine urine analyses from 4 patients after valve replacement, none of whom had hematuria prior to operation, were reviewed. After

*Late onset [illegible] bacterial endocarditis has occurred after 1 [illegible] at the [illegible] (Patient 11 [illegible] cardiac catheterization, and [illegible] self-administered injections in [illegible] drug addict.

Transvenous pacing

A seven-year review

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I. Historical development of transvenous pacing

Transvenous endocardial stimulation of the right ventricle was an extension of the technique of right-sided cardiac catheterization and the earlier description of sino-auricular stimulation and of direct myocardial stimulation.[1-3]

Rapid evolution of the technique followed its initial description in 1958, as it became apparent that prolonged periods of pacing could be employed for clinical control of patients with symptomatic heart block.[4]

At first, a unipolar catheter system was utilized with the negative terminal in contact with the endocardium and the positive terminal grounded to the skin. The development of an intraventricular bipolar catheter[5] allowed greater ease in myocardial stimulation because of a less critical position of the catheter and avoidance of the frequently infected and troublesome cutaneous ground wire.[6]

During the initial phase of study of internal electrical control of heart block, it became obvious that many patients who survived the acute episode required long-term stimulation of the heart. Although many of these patients were eventually managed with implanted pacemaker units, there were those who could not or would not undergo operative implantation. These patients were maintained on transvenous pacemaker stimulation for long periods. Large groups of patients who have been maintained on transvenous cardiac stimulation and totally implanted power packs have also been described.[7,8] This approach augurs well for the prolonged maintenance of patients who are too ill or aged to undergo thoracotomy safely.

II. Indications for transvenous pacemaker therapy for control of complete heart block

1. Initial control of the critically ill patient with heart block complicating acute myocardial infarction. The threat to life in these patients is more a function of heart block than of myocardial destruction. Surgical implantation during the acute episode is dangerous and may not be necessary because of the transient nature of the

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heart block. Application of external stimuli except in the immediate period after the onset of heart block is far from satisfactory. Under these circumstances the technique of transvenous pacing is ideally suited to the maintenance of absolute control over the patient's disease while awaiting recuperation from either cardiac or cerebral damage.[9]

2 *Establishment of absolute control of the heart rate during surgery.* These patients present with two distinct surgical problems (a) Patients with asymptomatic complete heart block who do not require artificial cardiac stimulation under normal circumstances may require pacemaker support during surgery for an unrelated condition. (b) Patients who require operative implantation of a pacemaker are unstable even with Isuprel support. By means of transvenous pacing they can be carried through surgical implantation with a sustained regular rate, with neither the muscular twitching of external stimulation nor the presence of percutaneously inserted myocardial wires.[10]

3 *Control during periods of implant failure and periods of prolonged reconstruction after infection of an implant.* Implant failures because of breakage of wires, infection, electronic or battery problems occur not infrequently. At these times interval transvenous pacing is required until repair can be effected. Where empyema or other intrathoracic or extrathoracic infection accompanies pacemaker failure, operative replacement is obviously contraindicated and prolonged periods of ambulatory, often outpatient, catheter pacing are necessary for rehabilitation.

4 *Management of complete heart block with complicating congestive heart failure.* Increase of cardiac rate to normal levels has been demonstrated to be effective in the control of congestive heart failure complicating complete heart block. These patients cannot tolerate prolonged external pacing and operative implantation is unsafe. Transvenous pacing, easily accomplished even under unfavorable circumstances, will effect control.[11] The optimal rate for best maintenance can be determined with measurements of cardiac output. Studies of cardiac output can determine the range of increase in cardiac output as a function of increase in rate and thus the feasibility of utilization of an atrial synchronous pacemaker. Occasionally a patient who is comfortable at lower cardiac rates (60 to 70 beats per minute) develops angina and/or a lowered cardiac output at elevated rates.[12] A synchronous pacemaker would thus be contraindicated.

5 *Patients who cannot or will not undergo operative implantation.* The very young with congenital heart block complicating other congenital heart disease and requiring a delay prior to definitive repair and the very elderly in whom thoracotomy would pose a major threat to life (ninth and tenth decades) can benefit from prolonged periods of transvenous therapy. In the latter group, permanent transvenous management may be the preferred mode of therapy.

There is a small group of patients who absolutely refuse surgery. They can be managed with a transvenous assembly.[13]

6 *Patients who revert to a conducted rhythm after a brief period of pacer therapy.* A relatively constant group of some 10 per cent of all patients seen with complete heart block and Stokes-Adams seizures return to regular sinus rhythm or other supraventricular rhythm. It is for this reason, in addition to others mentioned and implied, that a delay, usually of several weeks, is required prior to implantation. During this period most patients who are to revert will have done so.

Technique

The patient is placed in the recumbent position, the head is turned to the left, and the right shoulder is elevated. The root of the neck is cleansed and the external jugular vein is exposed. An ECG monitor recorder and manually operated external pacemaker strapped to the chest assure control of any acute asystolic episode during the procedure itself.

The pacemaker catheter is inserted under sterile conditions, preferably into the right external jugular vein. A vein in an upper extremity is unsatisfactory because of extensive motion of the catheter with motion of the arm. Should the right external jugular vein be too small or unavailable for any reason, a second choice is the left external jugular vein. The third

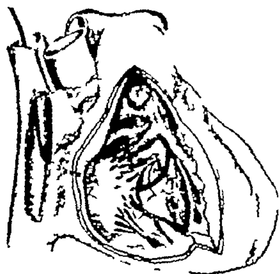


Fig. 1 The bipolar catheter as usually introduced, enters the heart via the superior vena cava, traverses the right atrium and tricuspid valve to be with its electrode in the proximal portion of the right ventricular outflow tract

choice is the internal jugular or cephalic vein either right or left Either of the internal jugular veins can be sacrificed with impunity (although both may not be sacrificed simultaneously)[14] If the internal jugular vein is to be used either of two approaches is feasible a lateral venotomy with a purse-string suture surrounding the catheter entrance, with preservation of the vessel or sacrifice by ligation of the internal jugular vein cephalad to the point of insertion of the catheter (See Figs. 1 and 2)

The catheter used is a No. 5 or No 6 bipolar electrode catheter* It is introduced into the vein and its progress through the superior vena cava, the right atrium and eventually into the main pulmonary artery is directed fluoroscopically From this position it is withdrawn slowly into the mid right ventricle, where pacing will be stable, and where the slight motion that is inevitable will not displace the catheter electrodes into either the right atrium or the pulmonary artery from which sites *stimulation is impossible.* When especially rapid placement is indicated a Teflon* Longdwell Escher" needle is introduced into the right femoral vein and the catheter *is passed through* it and into the right ventricle.[15] However when adequate control allows a somewhat more lengthy procedure, the right external jugular vein is used because of greater sterility of that site the possibility of greater duration of usage and stability of position of the catheter (See Fig 3)

With proper placement, stimulation should be possible at an output of approximately 1 milliampere, although some patients will require up to 2.5 milliamperes at threshold If more current is required one can be confident that the catheter is incorrectly positioned for optimal stimulation A position too close to the tricuspid valve is inherently unstable, since the tip *may be displaced proximally into the right* atrium An even more unstable position is high in the outflow tract of the right ventricle, from which site expiration may advance the tip into the main pulmonary artery where stimulation will once again cease. No loop or tension angle is to be left in the catheter course since straightening of the catheter will usually cause malposition of the tip and result in malfunction Once inserted the catheter is connected to the terminals of an external battery-operated pacemaker Only battery operated units are used for internal stimulation in order to obviate the possibility of ventricular fibrillation secondary to a leak of alternating 60-cycle current.[4,24]

The minimal flow of current for consistent stimulation is determined and the unit is set at about double the threshold level A satisfactory rate is set usually 70 beats per minute although a more rapid rate is selected when ventricular fibrillation is the mechanism for circulatory arrest, and suppression of all ectopic foci is necessary

The catheter is sutured into place with two No. 00 braided stainless steel sutures (1 centimeter apart) and both are anchored into the subcutaneous tissue at the site of insertion. The skin is closed over the steel retention sutures with interrupted silk sutures, and a light dressing is applied

*No. C31 U S Catheter Co., Glens Falls, N. Y

*E. I. duPont de Nemours & Co., Inc., Wilmington, Del.
†Becton, Dickinson & Co., Rutherford, N. J.







Fig. 2. A, B, and C. As the catheter is customarily introduced in the right external jugular vein it lies in the outflow tract of the right ventricle. The catheter should lie with the tip directed toward the outflow tract and with no tension angles or loose loops visible on the posteroanterior film. On the lateral projection the catheter will be seen to sweep anteriorly into the retrosternal position with the tip directed toward the outflow tract.

The pacemaker is then suspended from the neck, and supported about the thorax. The patient is returned to his room and given antibiotics but neither Isuprel nor anticoagulants. Digitalis and diuretics may be administered if indicated for control of congestive heart failure. Quinidine may be administered if multifocal premature ventricular contractions occur.

Results of therapy. At this institution 110 patients have undergone transvenous stimulation of the right ventricular endo-







Fig. 3. A, B and C. Emergency introduction of the pacemaker catheter via the femoral vein causes the catheter to traverse the inferior vena cava, right atrium, and the tricuspid valve and lie near the apex of the right ventricle. The Teflon needle through which the catheter is introduced remains on the catheter until pacing is terminated. The posteroanterior projection shows the tip of the catheter pointing toward the right ventricular apex, and the lateral projection demonstrates that, unlike in the jugular approach, the tip is not oriented anteriorly and superiorly but lies in the vicinity of the right ventricular apex.

cardium in the 7 years since the technique was initially described. These patients have had a pacemaker catheter in place for periods ranging between 2 hours and 5 years.

The first patient paced was supported for 2 hours during a major surgical procedure at the successful conclusion of which he returned to a stable complete heart block. He died during a Stokes-Adams seizure 12 days later having returned to his pre paced state in the interim. The second patient required pacing for 3 months, and again 18 months later for another 4 months. He finally succumbed to hepatitis without a catheter in place, after having had an indwelling electrode catheter for a total of 7 months.

Successive patients have had indwelling catheters for long or short periods of time as seemed to be appropriate. Five persons catheterized for only several hours underwent studies of cardiac output and since they had neither Stokes-Adams seizures nor congestive heart failure, prolonged pacing was not undertaken. Four other patients have stoutly refused operative implant and have been managed for more than 3 or 4 years on catheter only.

Three patients have been so managed for more than 4 years and 3 for more than 3 years. One of these patients died after an operative pacer implant. Nine were maintained for more than 2 years. One of these has undergone successful implant, and one has died of myocardial infarction during maintenance. Twelve patients have been controlled transvenously for over 1 year. One of these has successfully undergone implantation. Nineteen patients were managed for shorter terms, since in each instance early operative intervention was undertaken. (See Table I.)

Seven patients on catheter management have returned to permanent supraventricular rhythm after several months of transvenous pacing and have required no further electrical support.

Ten patients required catheter management during surgical repair of breakage of a lead or during treatment of an implant infection which precluded immediate reimplantation.

There has been a substantial group of patients who were poor operative risks

Table I. Duration of catheter stimulation

Duration	*Patients alive*	*Patients died during catheter maintenance*	*Total*
Less than 1 day	7	6	13
1 day–1 month	19	13	32
1 month–1 year	24	14	38
1 year–2 years	8	4	12
2 years–3 year	8	1	9
3 years–4 years	2	1	3
4+ years	2	1	3

Table II

Total catheterized for transvenous pacing	110
Total now alive	63
Dead of all causes	47
Total discharged after initial hospitalization	88
Total discharged on catheter maintenance	66
Total alive solely with catheter pacing or without pacemaker	31
Presently alive on transvenous pacing	23
Maintained on catheter pacing in excess of 1 month	63
Dead of all causes during prolonged pacing	15
Total implants	39
Dead after implantation	7
Implants now alive	32
Implanted during initial hospitalization	14
Implanted after prolonged transvenous control	25
Catheterized and paced briefly for study	5
Pacing discontinued because of return to stable supraventricular rhythm	5

debilitated or of advanced age (ninth and tenth decades) and were not subjected to a major thoracotomy. There was another group of patients for whom surgery offered a major psychologic threat and who refused operative intervention. These patients were managed successfully for prolonged periods on transvenous pacing. (See Table II.)

Complications

Complications of long term transvenous pacemaker therapy fell into four major categories.

1. Infection. Although approximately one third of all patients, at one time or

another developed mild to moderate inflammation at the site of entrance of the catheter into the external jugular vein such an event occurred only after weeks or months of catheter pacing These areas invariably responded rapidly to local therapy If the catheter became infected along its course and did not respond immediately to antibiotic therapy nothing short of removal and reinsertion from another site sufficed Nine patients have required eleven replacements, but only three of these have occurred in the past 2 years.

2 *Breakage of catheter conductive element* No catheter has ever fragmented in situ No foreign bodies have been left within the vascular system The bipolar catheter* currently in use has two conductive elements, a braided stainless steel wire and a single-strand copper wire Although the stainless steel wire has not to our knowledge broken the copper wire has. The two wires have also spontaneously short circuited These situations have usually been corrected by immediate conversion to a unipolar system utilizing a cutaneous ground wire.

3 *Malposition either intraventricular or extraventricular* With proper placement of the tip of the bipolar catheter in the mid outflow tract of the right ventricle insertion from the external jugular vein and proper fastening at the skin level malpositions have become uncommon The usual causes of malposition have been inadequate initial placement loosening of the subcutaneous stay sutures and placement of the catheter from the arm A capacious right ventricle occasionally has allowed the catheter to float away from the ventricular wall and cause intermittent stimulation Such a situation has, at times, forced an early implantation of a pacemaker Placement from the arm has become obsolete

4 *Perforation of the heart* Only one perforation by a pacer electrode has been observed This occurred in the fifth patient in this series after motion of the patient s arm through which the catheter had been inserted Veins of the upper extremities are no longer employed for this type of installation

*No. C51 U. S. Catheter Co.

Mortality

Transvenous stimulation of the heart has become established as a standard technique for the management of complete heart block. It has been of major advantage for the early therapy of the patient with Stokes-Adams seizures, since it not only has allowed rapid complete control of cardiac rate but has done so with safety unmatched by external stimulation or early operative implantation

Long term management of patients with a transvenous pacemaker has also proved itself to have a morbidity and mortality in selected patients similar to that of a total implant The higher mortality figures reported herein resulted from the presentation of a totally unselected series including many patients who could never have been considered for implantation The technique is simple rapid and can be performed with a good standard fluoroscope, an electrocardiograph a battery powered pacemaker and simple surgical instruments

The 110 patients catheterized during the past 7 years may be divided into three major groups. The first group encompassed those patients catheterized via a vein in an upper extremity and/or with use of a A C -operated pacemaker Both of these approaches are obsolete One death in this series can be attributed to cardiac perforation secondary to vigorous motion of the patient s arm 3 deaths were the result of a leak of 60-cycle A C that produced ventricular fibrillation and 5 deaths followed cessation of transvenous pacing This group ended with the thirteenth patient catheterized The other 4 patients of this group included 3 who survived 2 years and 1 who survived 4 years.

The second group of 18 patients was electively sustained on catheter pacing pending confirmation of the success of implantation techniques. The third and more recent group is one in which catheter stimulation has been used as part of an inclusive approach directed toward the management of complete heart block.

Sixty three of the 110 patients are now alive Twenty three are currently maintained on long term catheter management Thirty two have had implants of one or another design

The 47 dead can be categorized as fol

lows (1) Dead while not being paced—10 patients. Number one and number two in the entire series had catheters withdrawn prior to realization of the long term potential of endocardial stimulation Two children with surgically induced complete heart block with rapid idioventricular rates were not permanently paced transvenously and died suddenly One patient died of a myocardial infarction 3 months after return to regular sinus rhythm and termination of transvenous pacing Two early patients succumbed without pacing the second several days after she herself had removed the catheter and pacer assembly (2) Dead after ventricular fibrillation occasioned by 60-cycle A C leak—3 patients. Only these 3 patients have succumbed because of a complication of the procedure of catheter insertion (3) Dead after cardiac perforation and tamponade—1 patient. (4) Dead after operative implantation of a pacemaker—7 patients. (5) Dead of acute myocardial infarction and complicating heart block in which despite successful pacing cardiac failure occurred—5 patients. (6) Dead of unknown causes while being paced successfully—15 patients. (7) Dead of unrelated disease, i.e. respiratory failure, renal failure or brain tumor—4 patients. (8) Dead as a result of an infected catheter and bacteremia—2 patients. (See Table III)

Of the 110 patients, 32 were maintained with transvenous pacing for more than 1 month 38 between 1 month and 1 year 12 for 1 to 2 years, and 12 between 2 and 4 years. Two patients are now alive and well in excess of 5 years.

Table III *Deaths (all causes)*

Cardiac perforation	1
Cardiac arrest after cessation of transvenous pacing	7
While on implanted pacemaker	7
Progressive cardiac deterioration	5
Unrelated disease (respiratory failure renal failure brain tumor)	4
Congenital or postsurgical heart block	3
Ventricular fibrillation secondary to 60-cycle A.C. leak	3
Sudden death during long-term catheter maintenance	15
Bacteremia	2

Table IV

Years	Age distribution
0–9	3
10–19	2
20–29	1
30–39	2
40–49	
50–59	12
60–69	37
70–79	38
80–89	8

At the present time, of those patients surviving the acute Stokes-Adams episode who have been maintained on long term transvenous pacing and who neither have been electively implanted nor have reverted to a spontaneous rhythm 23 are still alive and well (See Table IV)

Summary

The short term and long term results of transvenous catheter pacing in 110 patients have been presented A discussion of techniques and the indications for transvenous pacing have been outlined

Transvenous pacing of the heart via right ventricular endocardial stimulation is simple, rapid and safe The complications of infection breakage of conductive leads, malposition and cardiac perforation have all become relatively uncommon with greater experience and affect a smaller and decreasing number of patients. The approach offers a continued promise particularly as improved material becomes available

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

Antianginal drugs.

Part II. Human pharmacology of nitroglycerin

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Nitroglycerin is the antianginal drug that is most widely used and most generally accepted as clinically effective. It is the prototype of a class of inorganic nitrite and organic nitrate congeners. Sodium nitrite, amyl nitrite, ethyl nitrite, erythritol tetranitrate, pentaerythritol nitrate, isosorbide dinitrate, and other organic nitrates share many important pharmacologic properties of nitroglycerin.

Nitroglycerin (glyceryl trinitrate) is a smooth muscle relaxant with predominant direct cellular action. It causes relaxation of most smooth muscles of the body, including bronchial, biliary, ureteral, uterine, and gastrointestinal. The possible exception is that of the small intestine. The most important pharmacologic effects are seen on the vascular musculature.

Vascular effects. The drug dilates all large arteries, such as the temporal, radial, and coronary arteries, as well as arterioles, capillaries, and venules. The most marked effect is seen in the postarteriolar bed, as has been confirmed in the skin, retinal, meningeal, and splanchnic circulations. Nitroglycerin is thus a universal vasodilator. As a vasodilator it causes a drop in blood pressure, more prominently systolic than diastolic, and results in a diminution of the pulse pressure. In the hypertensive individual there is a greater absolute drop in blood pressure than in the normotensive individual; this effect is also longer in duration. As a result of vasodilatation, venous return may diminish, resulting in diminution of cardiac output and stroke volume and a secondary increase in heart rate. The drop in systolic pressure and stroke volume temporarily reduces the work of the heart. This has been the basis for the presumed usefulness of this agent in the treatment of the paroxysmal dyspnea of acute left ventricular failure. In the hypersensitive subject, or in one to whom an excessive dose is administered, the decrease in venous return may lead to marked hypotension, which in turn can cause syncope. The latter subsides when the subject assumes the horizontal position and increases venous return.

Effect on the coronary circulation and on cardiac dynamics. In the normal subject or in subjects with mild cardiac disease who are *devoid* of coronary artery disease, nitroglycerin produces an increase in coronary blood flow which, on the average, amounts to 50 per cent of the resting value and an increase in myocardial oxygen consumption; the A-V oxygen difference remains unchanged. The coronary diastolic vascular resistance drops, as does the aortic

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blood pressure the heart rate increases, the pulmonary capillary and right atrial pressures drop indicating diminution of filling of both sides of the heart left ventricular work decreases, and an increase in the expenditure of myocardial energy for the generation of pressure occurs.

By contrast in the patient with significant coronary *atherosclerosis* nitroglycerin usually produces a drop in coronary blood flow Either a modest increase or a decrease or no change can occur depending on the individual patient Furthermore no change in coronary vascular resistance is noted *the myocardial oxygen consumption is* lowered the blood pressure decreases more than in the normal control group and the heart rate shows no significant change The cardiac filling pressures and work decline as in the normal individual The ratio of pressure generated to oxygen cost is basically unchanged

These findings contradict those of coronary cineangiography which seem to demonstrate that nitroglycerin induces vasodilation of sclerosed coronaries The hemodynamic findings described above which resulted from coronary sinus catheterization studies must be considered to be more valid since cineangiography does not measure blood flow it only demonstrates changes in the caliber of a vessel On the basis of radioisotopic precordial measurements, it is stated that nitroglycerin improves coronary blood flow The method is so gross that the validity of these observations must be questioned Furthermore it does not differentiate which coronary branches, whether healthy or diseased are responding to the drug In view of the responsiveness of a normal coronary artery to nitroglycerin and the apparent absence of response in the atherosclerotic artery one may properly ask whether diversion of blood flow to the less diseased coronary arterial bed where it is least needed may not be fostered by the administration of this drug It remains to be explained why in diseased coronary arteries, which remain unresponsive to nitroglycerin the arterial flow can be increased by effort

Electrocardiogram The electrocardiogram is unchanged by nitroglycerin In the hypertensive subject who demonstrates a left ventricular strain pattern the drug can produce minimal changes toward normality In the unusual patient with the so-called reproducible Master's two-step test nitroglycerin administered prophylactically can diminish or prevent the appearance of the S-T segment depressions seen after exercise. In the usual patient with coronary atherosclerosis who on exercise manifests a positive two-step electrocardiographic test this effect cannot be demonstrated on a statistically significant basis It is difficult to assign pharmacologic significance to these observations. Thus although all these data are inconclusive *and subject to variable interpretation it* seems to be likely that whatever beneficial effect nitroglycerin exerts on angina pectoris is due to a reduction in the work of the heart rather than to an increase in its blood supply

Absorption and metabolism Nitroglycerin is more effectively absorbed sublingually than orally When given sublingually the drug appears in the blood in about 2 minutes, its level in the blood reaches a plateau in 4 minutes begins to disappear by the tenth minute and is virtually dissipated by the fifteenth minute Gauged by vasodepression the vasodilating effect does not correlate perfectly with levels of the drug in the blood Thus, the drug induces an onset of fall in blood pressure in 1 to 5 minutes, a maximum fall in 5 to 10 minutes, and a return to the initial blood pressure within 15 to 40 minutes.

The fate of the drug in the body is unknown approximately 60 to 70 per cent of it disappears from the body and cannot be traced There is much evidence to support the contention that the pharmacologic effect of nitroglycerin is due to the organic nitrate per se rather than to its conversion to a nitrite. Little is known of the basic metabolic effects of nitroglycerin It has been stated that oxidative phosphorylation is inhibited by the nitrates. This may account for the apparent wasting of oxygen found in coronary sinus catheterization studies

Side effects and toxicity Nitroglycerin is unusually safe when used in recommended doses, but should be used with caution in patients with incipient glaucoma because of the possibility of producing a

rise in intraocular pressure Headache, by far the most common complaint is transient with nitroglycerin but can be protracted and severe with the longer-acting nitrates it appears to be related to dosage Methemoglobinemia is not a clinical problem with this drug

Tolerance It appears to be well established that with the continuous administration of nitroglycerin the pharmacodynamic effects diminish to the point at which the patient can accept progressively larger doses of the nitrate without evincing any side effects. This also holds for other nitrates and nitrites. The mechanism of the development of tolerance is unknown. However cross-tolerance between drugs of this group is known to develop Discontinuance of the drug restores the original sensitivity of the individual This tolerance is often disregarded in clinical use of short-acting and long acting nitrates.

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Annotations

Aortography in hypertension

The experimental work of Goldblatt and associates[1] and Wilson and Byrom[2] established the relationship between hypertension and renal ischemia and paved the way for surgical treatment in selected patients. Ischemia of the kidney can be diagnosed by intravenous pyelography, radioactive scanning, and split renal function tests, and since the development of abdominal aortography in the early nineteen-fifties it has been possible to demonstrate lesions of the renal arteries which might be producing ischemia. The aim of surgical treatment is either to improve the supply of blood to the kidney by arterial reconstruction or to remove the ischemic tissue. DeBakey and associates, using arterial reconstruction, report a rate of cure of 80 per cent in a series of 225 patients, and Smithwick and associates have obtained good results with nephrectomy.

In our hospital group 114 hypertensive patients have been investigated by abdominal aortography in the last 6 years, 108 by percutaneous transfemoral catheterization[3] and 6 by translumbar puncture. The criteria for case selection were based on those of McMichael. Seventy-nine of the examinations demonstrated normal renal arteries. The findings in the other 35 were: unilateral main or accessory renal artery stenosis (22), bilateral stenosis (1), fibromuscular hyperplasia (2), unilateral thrombosis (1), localized cortical loss without pyelonephritis (6), pyelonephritis (3).

Nine patients were considered to be suitable for operation. Aortorenal bypass grafts were inserted in 3 patients, using Dacron in 1 and saphenous vein in 2. Two died, one from heart failure and malignant hypertension after 18 months, and the other from acute renal failure 2 months postoperatively due to thrombosis of the vein graft and malignant hypertension. The third patient, who has been followed for 6 months, is still hypertensive and requires hypotensive drugs. Endarterectomy with patch angioplasty was performed in 2 patients and endarterectomy alone in 1. They have been observed for 3 years, 1 year and 9 months respectively; all are still hypertensive, requiring medical treatment. One of them developed acute abdominal pain 2 months postoperatively and a further aortogram showed thrombosis of the repaired renal artery. Nephrectomy was performed in 3 patients in whom a reconstructive procedure was not technically feasible. Two had severe peripheral vascular disease in addition to renal artery stenosis; the third had fibromuscular hyperplasia. All are still hypertensive after 2 or more years follow-up, and 1 is in congestive heart failure. Renal biopsy specimens were taken during operation in 5 patients. Hypertensive changes were present in both kidneys in 4. In the fifth, the microscopic appearances were normal distal to the stenosis, but changes of malignant hypertension were present in the opposite kidney. Thus of 114 patients subjected to aortography, 9 were considered to be suitable for surgery. Two of these died as a direct result of the operation and the other 7 still have hypertension requiring hypotensive drugs. Renal biopsies from the opposite kidney in 5 patients showed changes which were presumably irreversible.

Theoretically, the ideal patient is one who has hypertension of recent onset resulting entirely from narrowing of one or both renal arteries. A successful outcome to surgery cannot be expected unless the kidneys are histologically normal or have reversible arteriolar changes. In the present state of our knowledge the distinction between reversible and irreversible changes cannot be made. Vertes and associates obtained renal biopsy specimens from 52 hypertensive patients who were being considered for surgical treatment. Renal artery stenosis was demonstrated in 20. In the rest the renal arteries were normal, but arteriolar changes were present in both kidneys in every patient.

These results are not encouraging and suggest that the prognosis of the hypertensive patient is not improved by operation. Similar views were expressed in a recent article by Chamberlain and Gleeson. There is now a reluctance on the part of physicians to refer patients for aortography and of surgeons to attempt operation. Patients with pyelographic or other evidence of renal ischemia are now referred for aortography only if their hypertension is known to be of recent onset.

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The brachial arterial pulse pressure curve in the evaluation of valvular aortic stenosis

A recent paper by Delman and associates evaluating the usefulness of the brachial arterial pulse curve in identifying patients with severe valvular aortic stenosis concluded that valvular aortic stenosis could be identified from analysis of the upstroke time, the upstroke velocity, and the systolic ejection time and, furthermore, that patients with significant obstruction could be distinguished from those without significant obstruction. Their criteria for severe aortic stenosis included (1) upstroke time equal to or greater than 0.18 second, (2) upstroke velocity less than 600 mm. Hg per second, and (3) systolic ejection time equal to or greater than (0.092 × R-R interval + 0.21) seconds. Although they found that the rate-correlated systolic ejection time was a good screening test for the presence of aortic stenosis, it did not separate mild from severe cases. An upstroke time of less than 0.18 second or an upstroke velocity of more than 600 mm. Hg per second suggested to them the absence of severe aortic stenosis. Because left heart catheterization is not without serious complications, any simpler method of evaluating the severity of aortic stenosis would be welcomed. Data from 3 patients seen by our unit in the past month suggest that such analysis of peripheral arterial pulse tracings is not so helpful as the above mentioned authors indicate.

In our first case, an obese 43-year-old woman, upstroke time was 0.13 second, upstroke velocity 830 mm. Hg per second, and systolic ejection time 0.28 second (rate 90). Cardiac index was 2.1, left ventricular pressure was 310 mm. Hg, and the aortic valve area was calculated to be .33 cm.

In the second case, a 65-year-old man, upstroke time was 0.15 second, upstroke velocity was 1,800 mm. Hg per second, and systolic ejection time was 0.29 second (rate 89). Cardiac index was 3, left ventricular pressure was 270 mm. Hg, and the aortic valve area was .56 cm.

In the third case, a 65-year-old woman, upstroke time was 0.14 second, upstroke velocity was 860 mm. Hg per second, and systolic ejection time was 0.22 second (rate 90). Retrograde catheterization was unsuccessful. The patient developed cardiac arrest shortly after this attempt was discontinued. Pressures and cardiac output during attempted resuscitation gave a calculated aortic valve area of .5 cm.

At operation (Cases 1 and 2) or autopsy (Case 3), all patients were proved to have severe calcific valvular aortic stenosis. If the criteria of Delman and associates were valid, normal upstroke time and upstroke velocity with slightly prolonged ejection time in the first two cases would suggest mild aortic stenosis, whereas normal values for all three measurements in Case 3 would suggest the absence of aortic valve disease. During this period only 4 other patients with isolated valvular aortic stenosis have been studied. In 2 children no brachial arterial tracings were obtained. One 42-year-old man with very mild aortic stenosis showed normal values for the three measurements. A 60-year-old man with severe aortic stenosis had an upstroke time of 0.18 second, an upstroke velocity of 390 mm. Hg per second, and an ejection time of 0.29 second at a rate of 64.

The findings in our patients suggest that

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hazardous to draw conclusions about the presence or severity of valvular aortic stenosis from an analysis of the arterial pulse pressure alone. These findings are consistent with previous studies.

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On resting the human heart

Like any other organ the diseased heart repairs and returns to good health most quickly when it is allowed to rest. Obviously, the heart must continue to perform work even when it is diseased. Nevertheless, it is possible, within limits, to unload and thereby *rest the heart* by means of relatively simple measures which are available to all physicians. Thus, the physician may rest the heart by (1) decreasing the heart rate, (2) decreasing the arterial blood pressure, (3) decreasing the cardiac output, (4) decreasing the size of the heart, and (5) decreasing the velocity of myocardial contraction.

When the physician determines that it is necessary to rest the heart of his patient, he should strive to achieve as many of the factors listed above as is practical. Obviously, for each of the factors as well as for each patient there is an optimum value below which any *further* reductions may become deleterious. The physician should review each of the factors separately in terms of the patient in order to determine which apply to his patient and whether his therapy is adequate to modify a given factor. He should be aware that a particular agent may decrease one factor while increasing another. For example, digitalis may decrease heart rate and heart size but increase the velocity of myocardial contraction. On the other hand, complete bed rest decreases all of the above-listed factors.

Through bed rest and the judicious use of drugs it is possible to modify any or all of the factors listed above in the vast majority of patients—it is only necessary that the physician think of each of these factors when he outlines therapy for his patient. By applying these factors to each patient on an individual basis the physician avoids dangerous generalizations and gives meaning and direction to his therapy.

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Simultaneous recording of radiographic and physiologic data during cardiac catheterization

For the synthesis of physiologic and radiologic data during intravascular catheterization in animals and in patients, a composite of several electronic units was devised. Since this assemblage has provided useful data for many varieties of physiologic questions, we are presenting its plan.

A photograph of the basic components is shown in Fig. 1 and a diagram in Fig. 2. Strain gauges, *oximeter cuvettes, a pneumotachygraph screen, a* phonocardiographic microphone and lead for electrocardiograms, polarographic catheters, etc., are plugged into a junction box (*1*) from which shielded

Fig. 1 Photograph of assemblage of apparatus in the catheterization laboratory

Fig. 2 Diagram of composite assemblage of apparatus. 1 Strain gauges, cuvettes, microphone, ECG leads, etc. 2 Control unit. 3 Twelve-inch recorder (Waters Corp. G-12). 4 Seventeen-inch monitor oscilloscope (Sanborn Co., Model 769). 5 Image intensifier—Orthicon television camera (Westinghouse "Televex"). 6 Vidicon television camera (MTI—Westinghouse). 7 Synchronization (Westinghouse "Televex"). 8 Television monitor ( ). 9 Kinescope recorder (Federal Manufacturing and Engineering Co., Model K)

cables pass through conduits to control units in an adjacent room. Outputs are fed to mirror galvanometers and tracings may be recorded simultaneously on camera with 12-inch bromide paper. Outputs from the control units are also amplified by D.C. amplifiers and returned via conduits to a 17-inch monitor oscilloscope (4) in the laboratory which is faced by a Vidicon television camera (6) suspended from the ceiling. The output of the Vidicon camera is synchronized (7) with the output of the Orthicon television camera (5) which views the image-intensifier-fluoroscopic image from the subject. The fluoroscopic image on the television monitor (8) thus may have superimposed upon it the physiologic data which are appearing simultaneously at the recorder and monitor oscilloscope. Furthermore, this combined image may be recorded on the kinescope recorder (or on television tape).

We have found that these superimposed television images and/or the kinescope and tape recordings of these images are of considerable usefulness in several ways. During catheterization the operator may view the position of the catheter, the pressure at the tip of the catheter, and the electrocardiogram simultaneously, and may make kinescope or tape recordings of any pertinent event. The exact position of the catheter and the change in pressure across a valve, for example, may be recorded. In addition, composite kinescopic recordings of cardiac fluoroscopy and a phonocardiogram may be made. Furthermore, the precise timing of angiocardiographic frames with respect to the cardiac cycle may be determined from the superimposed electrocardiogram or, better, from an intraventricular or great vessel pressure tracing. In studies of ventricular volume by the angiographic technique, for example, the exact identification of end-diastolic and end-systolic frames is readily accomplished. Finally, indicator-dilution curves may be recorded simultaneously with angiocardiograms and intraventricular pressures.

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Letters to the Editor

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November 16 1965

To the Editor

I should like to comment on two poi ts in Dr Dall excellent and timely Annotation on Digitalis Intoxication," which appeared in the October 1965, issue of this JOURNAL (p 572).

1 The author tates that in cardiac failure occurring "as a secondary feature as in severe anemia, cor pulmonale and thyrotoxicosis, the results of digitalization are often disappointing and lead to excessive dosage, unless it is recognized that the same degree of slowing is not to be expected in these circumstances." To the less experienced this could imply that in heart failure due to primary cardiac disease a more substantial degree of slowing should be expected as an indication of effective dosage. It should be re-emphasized that effective digitalization in patients with sinus rhythm need not, and often does not, reduce the rate at all, or does so only to an insignificant extent. The iew that, in order to be effectiv digitalis must reduce the rate is one of the most prolific sources of over digitalization. I the writer opinion this is a misapplication, to patients with sinus rhythm of conditions prevailing in those w th atrial fibrillation and a high entricular rate where the slowing effect of digitalis is both pronounced and linically im portant

2. It is stated in the Annotation that in partial heart block, digitalis is contraindicated unless the failure is persistent despite bed rest and adequate diuretic therapy because of the risk of precipitating complete atrioventricular block." This tatement could with advantage be amended t include group of patients w th partial A V block *of varying degree* who tend to develop attacks of giddiness nd transient loss of consciousness at times when the degree of block varies. The condition of these pa tient ca sometimes be improved by onverting by means of digitalis the arying partial into persistent complete A V block This hould be done in hospital, and under ECG control Only small doses of digitalis are indicated, particularly if the patient is elderly for example digoxin, ½ tablet (⅛ mg) twice daily

A Schott M D

REFERENCE

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Royal Alexandra I firmary
P isley Scotland
December 7 1965

T the Editor

Dr Schott has raised two points of interest I think that most physicians would gree that in patient with sinus rh thm and cardiac failure the effect of digitalization is less obvious slowing of heart rat nd other linical features may signify succes of therapy such as relief of dyspnea diuresis or fall in jugular enous pressure If the heart rat does lter w th digitalization there are three possibilities

1 The myoc rdium is unable to respond further to the drug

2 There is complicating factor such as infection thyrotoxicosis or nemia, in addition to primary cardiac disease

3 The dose of digitalis has been pushed beyond the therapeutic optim m and is now producing the earliest sign of toxicity

Onl the physician i charge of each case evaluat these factors, and there is no rule of thumb but in factor 1 and 3 it is important to know that there has been adequate potassium medication t the same time as the administration of digitalis

The second poi t is one for the connoisseur I ha no personal experience of the measure that Dr Schott suggests in arying partial heart block but I would think that the success of such a maneuver would depend entirel on the entricular rate since the production of a stable complete heart block with digoxin may ll one little if a slow entricular rate results in Stokes-Adam ttacks

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To the Editor:

We have read both with delight and dismay the article entitled "The Physiologic Fallacy of Adjusting for Body Weight in Performance of the Master Two-Step Test" by L. B. Rowell and associates which appeared in the October, 1965, issue of the AMERICAN HEART JOURNAL: delight in that these eminent research workers are interested in the physiology of a common clinical exercise tolerance test, and dismay at the interpretation of the results of our published report and of their own efforts.

The authors quote the paper of Ford and Hellerstein as describing the oxygen consumption of the *double* Master test, whereas in reality Ford and Hellerstein dealt only with the single Master test. In fact, as was clearly stated in their report in 1961, Hellerstein and associates specifically note that in their clinical practice "The double standard test has been proscribed since it is our opinion that maximal or submaximal effort tests are contraindicated for patients with coronary disease except in special circumstances." The small discrepancies found by Dr. Rowell and associates in the oxygen cost of their double test on 10 adults and 4 children when compared with the values derived by Ford and Hellerstein on 85 healthy normal adults (1.740 ± 0.445 and 1.485 ± 0.44 liters of oxygen per minute, respectively) are probably due to the fact that a double test was being compared with a single test. The pronounced difference in sample size also may be a factor. The oxygen requirement per minute of the double test would be higher than that of the single test because the patient performing a single Master test is not yet in a steady state by the time he finishes the single test, and his oxygen requirement must still increase during the second 90 seconds of the double test.

Moreover, the data of Dr. Rowell and associates may be somewhat misleading. They state that the oxygen requirement of the double Master test ranged from 19.1 to 38.6 ml. per minute per kilogram of body weight, a difference of 102 per cent, and that the coefficient of variation of oxygen consumption per kilogram of body weight is much greater for the Master test than for a 40-step test (26.7 and 9.4 per cent, respectively). However, these figures were derived from data on 14 subjects, 4 of whom were only 12 or 14 years old. When the figures for these children are excluded and the values for the remaining 10 adult subjects (ranging in age from 19 to 27 years and in weight from 64.7 to 97.3 kilograms) are calculated, the mean oxygen consumption per kilogram of body weight during the double Master test is 23.73 ml. per kilogram of body weight per minute (standard deviation 2.36), ranging only from 19.6 to 26.7 ml. per kilogram of body weight per minute. When similar computations are made for the fixed 40-step test, the mean oxygen consumption per kilogram of body weight per minute is 21.9 (standard deviation 1.66), ranging from 19.7 to 25.2 ml. per kilogram of body weight per minute. The coefficient of variation of oxygen consumption per kilogram of body weight per minute is thus only 9.9 per cent for the double Master test and compares well with that of 7.6 per cent calculated similarly for the 40-step test. This demonstrates that for the adults tested the Master double-step test provides a relatively constant load after all, although it is slightly larger than that of the 40-step test, viz. 14.5 and 13.3 steps per minute and 23.73 and 21.92 ml. of oxygen per kilogram of body weight per minute, respectively.

There are two good reasons for excluding the children's values in making a comparison of the results of the two groups of investigators. First, Ford and Hellerstein dealt solely with adult subjects, none of whom weighed as little as 40 kilograms. Indeed, the Metropolitan Life Insurance Company's tables of desirable weight for men 25 years of age and over do not list weight below 112 pounds.

Second, the total energy cost of the Master two-step test for such children or for the rare adult who weighs 40 kilograms, admittedly, is less than that for average-sized adults, although the energy cost per kilogram of body weight is greater. The latter is due to a combination of factors: (1) the large number of ascents prescribed by Master and (2) the difficulty which a 14-year-old, 40-kilogram child has in traversing 2 nine-inch steps at the rapid rate required by the double Master test (60 ascents in 3 minutes), as compared with the slower rate of the 40-step test. The statements of Ford and Hellerstein concerning the equal energy cost of the Master test in adult subjects were not intended to apply to children. Indeed, since the test is used clinically almost exclusively for the evaluation of adults, particularly men over the age of 30 (not included in the sample of Dr. Rowell and associates), the physiologic response of children seems to be interesting but irrelevant.

Finally, one must remind Dr. Rowell and associates of the purpose of the Master two-step test as stated in our original reports.[3] The test is not used by us simply as a diagnostic tool for coronary heart disease, but rather it has been "*useful for prescribing work and daily activities* for patients with all types of heart disease."[2] Although we agree with Dr. Rowell and associates that a fixed step test provides a standard physiologic task, the test is of little help to an employer who is interested *not* in how much energy an individual must use per kilogram of body weight, but rather in the problem of *whether a worker can do a job or a specific task*. A lightweight individual performing a fixed 40-step test may have a normal oxygen uptake per kilogram of body weight but still be unable to perform a given job simply because the *total* oxygen requirements of the job are excessive. Therefore, an industrial physician using such a test would have some notion about the health of the employee but no idea whatsoever whether the worker, healthy or not, could perform a given job. However, the Master test, in which the total oxygen uptake is

similar for all adults, can easily help the physician to reach a conclusion about whether an individual has the capacity to perform a given task. Thus such a test when properly conducted could demonstrate that a lightweight, healthy individual might not be able to perform a job whereas a heavier cardiac patient might be able to perform the task perfectly well.

It is for these reasons that we think that the Master two-step test is still of use in determining the physical status of the adult cardiac patient who is a potential employee. However we recognize that the Master two-step test, like all other tests of cardiovascular function which employ only one level of work is not adequate to predict the electrocardiographic and heart rate responses of an individual at higher levels of work. Only a multilevel exercise tolerance test e.g. on a bicycle ergometer or a treadmill, can provide this information. Therefore for complete and accurate evaluation of the adult cardiac patient we recommend multilevel exercise testing.

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To the Editor:

We wish to thank Dr. Hellerstein and his colleagues for their comment concerning our recent paper entitled "The Physiologic Fallacy of Adjusting for Body Weight in Performance of the Master Two-Step Test," which appeared in the October 1965 issue of the AMERICAN HEART JOURNAL. We apologize to Dr. Ford and Dr. Hellerstein for the error in our article referring to their work on the double rather than the single Master's test.

Clearly we are in agreement on the major point of the paper, namely, that a fixed step test provides a standard physiologic task. We hope that the reasons for the necessity of this when applying the test for the purposes intended by Master and the multitude of physicians who use the test today are clear. These principles have been discussed by some of us elsewhere also.

We do not agree that such a standard physiologic task (i.e., fixed number of steps) is inapplicable for the special purpose stated by Hellerstein and associates specifically to test whether a worker can do a job or specific task. This depends entirely on the nature of the task. If the worker's task involves moving his body mass against gravity (i.e., walking, climbing stairs, carrying loads over distances, etc.), then the industrial physician must consider how much oxygen is consumed per kilogram of body weight. It is the worker's body weight which determines the cost. The physical work in many occupations involves this type of effort. Thus a *fixed task* requiring the same cost per kilogram of body weight for all subjects is the test of choice. Any test which is performed against the body mass cannot have *equal* cost among different individuals in these terms unless the load is *constant*.

Alternatively, if the worker's task does *not* require the movement of his body mass but rather an external load (i.e., lifting objects, pedaling a bicycle, etc.), then the oxygen cost is fixed by the external load and is independent of body weight within the limits set by maximal oxygen consumption. Since a step test requires work against body mass, it is *not* the test of choice for such an application. With some difficulty the test can be so scaled for body weight that the total cost is constant. As our data and that of Ford and Hellerstein show, the present scales *do not* achieve this. We will only to contrast these data with those of Ryhming who measured total oxygen consumption as subjects stepped up and down a 40-cm. step at fixed rate 22.5 times per minute. The coefficient of variation of the average response (30.5 ± 0.3 ml. of oxygen per kilogram of body weight) was only 1 per cent.

Total oxygen cost (liters per minute) is easily kept constant by testing subjects as they work against a fixed external load. Åstrand[4] demonstrated that over a wide range of external loads (300 to 900 k.p.m. per min. on the bicycle ergometer) the response at any given load is remarkably constant. The coefficient of variation ranged from only 1 to 2 per cent for either male or female subjects ranging in age from 20 to 68 years. This is in contrast to a coefficient of variation of 16.5 and 25.6 per cent in Ford and Hellerstein's data and in ours, respec-

tively where workload was supposedly equalized for different individuals by Master's scale.

Although it is not relevant to the major point in our paper, the main reason for the discrepancy between the magnitude of our average net oxygen cost and that of Ford and Hellerstein has been pointed out in their letter. They have also pointed out that the variability in the intake of oxygen per kilogram is still quite high for the fixed 40-step test. Indeed, when contrasted with Ryhming's results for a fixed-rate step test this is obvious. Since both Ryhming and we used the more accurate classic techniques for measurement and calculation of oxygen cost, the cause must be sought elsewhere. Subtraction of "nonbasal" resting oxygen consumption measured in seated and perhaps anxious *subjects just prior to the test certainly adds to the variability.* Resting oxygen consumption is quite variable under such conditions. The measurement of oxygen debt will cause even more variability, since magnitudes and rates of repayment differ in different individuals. Repayment can vary widely from apparent marked underpayment to marked overpayment. This has confused the results of both Ford and Hellerstein and our study as well as, we fear, the issue itself.

We agree, of course, that removal of the 4 light weight subjects (who indeed are children) decreases the variability in our measured responses to the Master test. Elimination of the 4 heavier subjects (89.4 to 97.3 kilograms) will decrease further the variability. Also, the similarity in age of our adult subjects would tend to decrease slightly the variability (by use of the age correction in Master's scale). However, the lightweight subjects *do not* increase the variability because they are children but rather because their body mass is small. Parenthetically, the number of steps required by Master for the 40-kilogram child 10 to 14 years old is 30 per 90 seconds whereas 29 steps are required of subjects 15 to 29 years old at this weight. Thus, *for an experimental test of the effect of body weight* on oxygen consumption during work, the inclusion of children 12 to 14 years old is entirely legitimate in the absence of significant changes in mechanical efficiency up to the age of 60 years. The reason for including the children was, of course, extension of the range of body weights. That actually Master's step test is rarely used in children has no bearing on the examination of the biologic validity of Master's correction for body weight in the step test. We would like to remind Dr. Hellerstein and associates that there are adult populations in the world whose average body weight is very small by our standards (many carry out occupations requiring heavy physical labor).

The expressed purpose of Ford and Hellerstein's original report was to indicate how severe an exertion the Master two-step test is as well as to compare its energy requirements with those of certain jobs. How severe a stress is 1.485 liters of oxygen per minute? The authors concluded: "The Master two-step test was found to have a sound physiological basis *especially since the stress it imposes* is comparable to the demands of the ordinary activities of life and *is constant for patients of different ages and weights.*" The authors appear to deny this conclusion in their letter when they assign the same test to demonstrate that a lightweight man might not be able to perform a job that a heavier man might do with ease. That is, the stress is much greater for the lighter man. Again, *this is our point.* Unfortunately, Dr. Hellerstein and associates have proposed a broad application of such a test to examine the capacity of men to do a job in industry. They have not considered the nature of the job.

In our article we stated another reason why a constant level of oxygen consumption (in liters per minute) does not comprise a *constant* stress for people of different ages and weight. Briefly, maximum intake of oxygen depends to a considerable degree upon body weight and age. The severity of work depends upon the percentage of maximum oxygen consumption required.

Finally, we would also argue about Ford and Hellerstein's interpretation of the stress in terms of physical work done in performing Master's test. Since the external work done in forward locomotion plus the cost of turning around was not computed, how do they justify an external work calculation which estimates a fraction (unknown) of the total external work done (see Erickson and associates)?

In analogy, our argument refutes the concept that, to make an equal contest in a foot race, the 50-kilogram man must run twice the distance required of a 100-kilogram man. Also, the absurdity of the contention that in locomotion equal physical work (i.e., transport of body weight) amounts to equal biologic load can be shown by comparison of animals of different body size, which is also a legitimate procedure of testing the validity of a biologic principle. A mouse weighing 25 grams would have to climb 50,000 meters in order to do the equivalent work of a horse weighing 250 kilograms climbing a hill of 50 meters.[7]

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To the Editor:

The recent article by Cosma, Levy, and Pipberger[1] proposes a rejection of the Wilson hypothesis of constant gradient in spite of changes in the ventricular activation path.[2,3] It appears reasonable that any sound test of this hypothesis demands that the changes in ventricular activation (ÂQRS) of whatever form be reasonably *free* from factors which are known to affect changes in the gradient $s\vec{G}$. Unfortunately, the PVC in the otherwise normal electrocardiogram (omitting the more risky abnormal ÂQRS) is certainly not such a test. The delicate pressure and temperature gradients across the ventricular wall have long been known as important factors which affect $s\vec{G}$;[3] in particular, there are the known changes in $s\vec{G}$ which are associated with any changes in cycle length. Since the PVC necessarily introduces change in cycle length (obviously *decreasing* the pressure gradient and introducing earlier the beat of contraction upon a diminished coronary blood flow), the changes in $s\vec{G}$ may be anticipated from the nature of the computer *input*.

This article may show that the PVC is associated with primary T-wave changes superimposed upon the obvious secondary T-wave changes, but I am unable to find any justification for rejection of the Wilson hypothesis. On the contrary, the results further support factors which have long been known to affect $s\vec{G}$.

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Book reviews

FUNDAMENTALS OF CARDIOPULMONARY RESUSCITATION. By James R. Jude, M.D., Professor of Surgery, University of Miami, and James O. Elam, M.D., Professor of Anesthesiology, University of Missouri. Philadelphia, 1965, F. A. Davis Company. 153 pages. Price $5.

This is a very good book by authors who developed and simplified the method of closed-chest cardiac massage and cardiac resuscitation. The book is well illustrated with simple diagrams, the legends are good, and the text is well written. The authors consider not only closed-chest massage but internal or open-chest massage as well. They describe the signs of cardiac arrest, the procedure to employ in diagnosis, methods of resuscitation and treatment, the use of the defibrillator, and aftercare of the cardiac patient including pulmonary problems after resuscitation. A good bibliography is included at the end of each chapter. The book is written to be of value to medical students, and even nurses, as well as to physicians.

NEUROGENIC HYPERTENSION. By C. J. Dickinson, D.M., Senior Lecturer in Medicine, University College Hospital Medical School, London, England. Oxford, 1965, Blackwell Scientific Publications. Philadelphia, 1965, F. A. Davis Co. 274 pages. Price $10.50.

This book presents a rather exhaustive review of the studies in experimental animals and man concerned with the relationship of the central nervous system to the regulation of arterial blood pressure. Dr. Dickinson has contributed to the understanding of the mechanisms regulating arterial blood pressure. He reviews the role of baroreceptors, especially the carotid sinuses, in regulating blood pressure and in the production of hypertension experimentally. The author takes the reader through the literature and leads him to his own interpretations of these studies, ending finally with his own hypothesis, that is, an increase in resistance (primarily in the large arteries to the hind brain) to blood flow in the brain (the medulla, in particular) may be responsible for the high arterial blood pressure in essential hypertension. Thus cerebral ischemia, not renal ischemia, is the important cause of essential hypertension. Although not a new concept, Dickinson develops the idea in his book by carefully selecting studies which support his hypotheses and ignoring to a large extent those which contradict the hypothesis. The main physiologic basis proposed is that blood must reach the brain, especially the vitally important centers, such as the respiratory, vasomotor, hypothalamic and others, in order for the animal to survive. If cerebral blood flow tends to decline, then neurogenic mechanisms supported by humoral ones increase the blood pressure in order to maintain a minimally adequate supply of blood to these centers. The author presents his case very well, but the reader is still convinced that the etiology of essential hypertension is still unknown, although he learns much from the book. This book does not settle the argument between Platt and Pickering, nor is this necessary or expected. Such points of view appear merely to be academic after one has read the book, which summarizes an enormous number of studies by many people over many years of work. However, the cause of essential hypertension has yet to be established.

This is a valuable book, but a little tiring to read. It should prove to be useful to anyone interested in the regulation of arterial blood pressure and in arterial hypertension.

CARDIAC AND VASCULAR DISORDERS. DIFFERENTIAL DIAGNOSIS BY NEW PHYSIOLOGICAL TECHNIQUES. By Prof. Dr. Rudolf Volker, University of Göttingen, Gottingen, Germany, with Prof. R. Schoen and Karlman Wasserman. Translated by Henry Mayer, M.D., Stanford University Medical School, Palo Alto, Calif. Second edition. Springfield, Ill., 1965, Charles C Thomas. 236 pages. Price $11.50.

This book by Dr. Volker is interesting and useful in a field which is much neglected today, i.e., diseases of the peripheral circulation. There are many excellent illustrations and a fairly good bibliography of German papers. However, in Chapter I, the author writes about "the volume pulse of the arterioles," when actually he cannot claim to be studying the changes in volume of only the arterioles of the digits. He shows digital volume plethysmograms which must certainly reflect changes in volume of all vessels in the digits. He also fails to define carefully the method used for recording plethysmograms. This is most important to the reader. The psychic state of the subject, the temperature of the atmosphere, and other factors which influence the behavior of the digital vessels are not emphasized adequately. These factors must be controlled if the plethysmogram is to be clinically useful. On the other hand, Dr. Volker does show how the volume waveform can change with disease. This book should stimulate interest in plethysmography, but the successful clinical application of this method requires expert supervision. The material is really not very critically presented, so that the inexperienced reader will have to turn to other works in the field before he can understand adequately the method and discussions presented.

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Editorial

Reflections on electrocardiography

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The amazing increase in the use of electrocardiography during the past three decades, with a more or less commensurate increase in the number of its practitioners, has made the admonition that long, arduous training in this field is necessary seem to be a bit old fashioned. The graduates of the popular short courses, and those who prepare themselves by reading the textbooks written for that purpose quickly find their new accomplishments useful because (1) most, but by no means all, abnormalities of cardiac mechanism are displayed with remarkable clarity, and (2) many of the changes in patterns resulting from cardiac damage could scarcely escape recognition. All practitioners have been indoctrinated in the gospel of the "Twelve Lead Electrocardiogram" and the almost universal stern disapproval of any deviation from this technique save for supplementary unipolar leads, or perhaps ventures into vectorcardiography. That the attitudes have become a bit more rigid than the situation warrants may deserve inquiry. The distinguished physicist Professor Bridgeman once thought it advisable to warn even such a scientifically trained group as young physicists not to accept dicta merely because they are frequently repeated.

Einthoven's original, rather offhand presentation of his equilateral triangle hypothesis suggests that this great investigator had in mind that hypotheses first proposed to account for newly discovered phenomena tend to be oversimplified. He was as well aware as any of the early critics of the hypothesis that some of the assumptions which he employed could be regarded as somewhat stretched approximations. But the later work in his laboratory on the "angle alpha" appeared to convince him as well as most others that he had been on the right track. It was not until many years later, after other experiments confirming those of Einthoven had appeared, that advances in the knowledge of bioelectrics made apparent the lack of relevance of these experiments.

For many years, there appeared to be no great interest in theory among electrocardiographers despite the countless equilateral triangles reproduced by authors to expound upon Einthoven's views. But when interest developed in localized damage to the myocardium by coronary disease and some of the achievements and deficiencies of Einthoven's technique were revealed, it seemed to be necessary to review that part of theory dealing with the representation upon the body surface of electrical activity arising in various parts of the heart. It was difficult to reconcile Einthoven's hypothesis with the ex-

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cellent electrocardiographic representation of damage in certain cardiac localities and not in others. Also difficult to reconcile were marked changes in Leads II and III with little or no change in Lead I or marked changes in Leads I and III with little or no change in Lead II. It seemed to be unlikely that vectors centering about the "electrical point" or what was later called the "equivalent single dipole" could behave throughout the ventricular complex in a manner that would produce either of the results mentioned above. An alternative explanation would be that the abnormal electrical activity was being mainly and sometimes entirely channeled into one or another of the three extremities and therefore being distributed in two of the three leads in accordance with the simple identity called Einthoven's law. If this were true, one might find electrical abnormality more or less channeled to other body surface areas, when Einthoven's leads failed to reflect lesions found at necropsy. The precordium was easily demonstrated to be such an area. At the same time, a new interest was introduced, namely, the patterns of fluctuations of potential in single areas, although doubtless this concept had been in the minds of investigators who had placed electrodes directly on the surface of the heart. Good clinical results could be obtained by pairing the precordial electrode with one of various distal positions, such as the extremities or even the back, but the inevitable differences in the patterns recorded led to uncertainty as to which would best display the precordial potentials. The late F. N. Wilson and his associates solved the problem to the satisfaction of believers in Einthoven's hypothesis with their unipolar leads. Experience with V precordial leads demonstrated that they are clinically useful and probably represent a more convenient arrangement of differences in potential than the CF leads which Wilson and many others had previously employed, even though some of Wilson's best original work was done with CF leads.

The few stubborn souls who refused to accept Wilson's solution of electrocardiographic technique and continued trial-and-error procedures of pairing electrodes finally nearly all gravitated to the use of CR precordial leads. One might ask to what extent these few recalcitrants are justified in adhering to CR leads. In many patients the differences between CR and V precordial lead patterns are slight enough to be unimportant clinically, although in some patients the differences may be great enough to have a bearing on diagnosis. The differences for any precordial area at any instant of time may be expressed as follows:

$$CR - V = \frac{2}{3}\left(\frac{\text{Lead I} + \text{Lead II}}{2}\right) = -\frac{2}{3}\,aV_R$$

Thus, with certain reservations concerning the QRS complex, one can usually get a fair idea from looking at either a CR or V precordial lead what the other would be like, provided that either Leads I and II or aV_R be available.

The above-mentioned identities account for the fact that when V and CR precordial leads are much alike, limb lead deflections are relatively small. They necessarily differ more when limb lead deflections are large. It becomes obvious why R and T precordial deflections in normal subjects tend to be of smaller amplitude in V leads, QS complexes in right precordial V leads are more frequently seen in normal subjects, R' is often found in right precordial V leads in association with a deep S deflection in Lead I, and Wilson's unexplained deflection in V_1 in right bundle branch block has approximately two thirds of the amplitude of the S wave in aV_R.

It is also obvious from the relationships stated above that two thirds of the algebraic mean for any changes that may occur in Leads I and II must be reflected in either CR or V precordial leads, or partly in both. To be able to answer this question quantitatively would decide which method came closer to the objective of recording the fluctuations in potential transmitted to the exploring precordial electrode. Observations indicate that changes sometimes occur in limb leads without discernible changes in CR precordial leads, practically all being channeled into the V precordial leads. Changes in limb leads of sufficient magnitude to be traced are always associated with changes in V precordial leads. Thus, all V precordial lead

patterns occasionally have a slightly abnormal appearance when all CR patterns remain unchanged as may occur in certain patients with acute posterior wall infarction of the left ventricle with large positive displacement of the S-T segment in Lead II. But in most patients with acute or chronic pericarditis acute or chronic ischemic heart disease, various myocardiopathies, and even the hyperventilation syndrome, CR precordial patterns look more abnormal than V patterns, as they also do when there are significant changes after an exercise test or after the administration of digitalis.

The relationships between CR and V precordial leads stated above do not enable one to decide which of the two is the "better" method of pairing with an exploring electrode. One should be able to do about equally well with either method if he bears in mind the reasons for their differences. Perhaps neither technique is the best possible; we should be asking ourselves whether better procedures can be devised. The intellectual climate of clinical electrocardiography has not been highly receptive to new ideas since the introduction of unipolar leads. After all one might well hesitate to exchange the supposedly concrete information recorded in unipolar leads for the less tangible values dependent upon the differences in potential between two unknown variables. Observations which cannot be reviewed here suggest that the distribution of potential upon the epicardial surface is a far more complicated affair than had once been thought and that the spread to body surfaces is still poorly understood. In fact it has been pointed out that if one assumes homogeneity of conduction throughout the body tissues, as Einthoven did, the influence of body configuration on the distribution of potentials, in so far as the body departs from a sphere, had not been taken into account. Finally, the demonstration more than 20 years ago of decrement of ventricular potentials with good preservation of patterns along certain lines points to a distribution far simpler and more easily comprehended than the complexity suggested by the unipolar procedure. The latter has led to the proliferation of many supplementary leads and to a widespread employment of vector-cardiography in the attempt to improve clinical diagnosis.

There are doubtlessly important inherent limitations in body surface electrocardiography. In fact it is easy to show by experiment that lesions capable of producing changes in intramyocardial leads may fail to produce recognizable changes in epicardial leads. But the possibility has not yet been excluded that some of the present limitations of body surface electrocardiography are not necessarily inherent, but may result from the crudity of the methods which we employ. It may be that less preoccupation with the past will encourage progress. The concept of planar distribution of potentials on the body surface although not exactly a new idea, is an outgrowth of the demonstration of lines of decrement of ventricular potential patterns. Because unipolar leads have proved to be an inferior method of demonstrating lines of decrement they have little usefulness in exploring the extent of planar versus other pathways of conduction. The significance of relatively small differences in potential within a large area in the right upper part of the body as compared with the left and the approximate isopotential below the level of the umbilicus urgently require explanation. The relationships between epicardial potentials and those of the overlying precordium and its vicinity remain obscure, unless the old idea favoring a close relationship proves to be correct. The situation has not been clarified by the arbitrary downgrading of proximal potentials in support of vectorcardiographic techniques.

The widespread complacency in the field of clinical electrocardiography and the belief that the Twelve Lead Electrocardiogram settles everything that can be settled might well be tempered by recognition of the fact that in the present stage of our knowledge, the assertion that a unipolar lead records merely the difference in potential between one unknown variable and the mean of the three other unknown variables cannot be successfully challenged.

Perhaps if students of electrocardiography were taught (1) the nature and limitations of the information they collect, (2) the empirically derived separation between the normal and abnormal for the

technique employed (3) how much of the supposedly abnormal is solidly based upon clinical and pathologic correlation and how much merely upon reasoning that certain relationships should exist (4) how conditions which bear little or no relation to heart disease produce changes sometimes difficult or impossible to differentiate from certain effects produced by heart disease then we would happily encounter fewer dogmatic erroneous interpretations. Assaults on the peace of mind and interference with work programs of those mistakenly convicted of heart disease would be diminished On the other hand the lack of recognition of minor significant changes or the placing too much emphasis on a normal electrocardiogram thus leading to failure to recognize early coronary disease should also be lessened That the number of such errors can and should be reduced quickly becomes apparent to any one with long and arduous training who reviews some of them

Clinical communications

Computer analysis of the kinetocardiogram from patients with atrial septal defects

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The purpose of this paper is to present some of the kinetocardiographic findings in patients with atrial septal defects as analyzed by a computer. The study describes certain changes in pattern as related to altered pulmonary arterial pressure and pulmonary vascular resistance. In addition, it will be shown that it is possible by computer analysis of the kinetocardiogram to predict whether the mean pulmonary arterial pressure is elevated.

Patients

Thirty-nine adult patients with the secundum type of atrial septal defects were included in the study. Those patients with endocardial cushion defects, mitral insufficiency, or other congenital abnormalities were eliminated. Three patients with partial anomalous pulmonary venous drainage into the right atrium were retained in the study, since the hemodynamics of this condition are identical with those of isolated atrial septal defects. In addition to the group of 39 patients listed above, 8 patients who were catheterized after the initial collection of the data were later added in order to test the value of the discriminant analysis, as will be discussed. The selection of patients was made solely on the availability of kinetocardiograms that were taken within 2 or 3 days of cardiac catheterization. The patients ranged in age between 14 and 62 years. There was no clinical evidence of concomitant ischemic heart disease in any patient, including those over 50 years of age.

Methods

All subjects were premedicated with sodium pentobarbital, and venous catheterization of the right heart was then performed. Pressures were measured with Statham strain gauges (P23\[illegible\]) and recorded on an Electronics for Medicine recorder. Mean pressures were determined by electrical integration and were calculated over a minimum of three respiratory cycles. The zero reference point was 10 cm. above the plane of the fluoroscopy table. Blood oxygen contents and capacities were determined by the method of Van Slyke. Oxygen consumption was determined by the collection of expired gas

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Table 1 Catheterization findings in the 47 patients studied

Patient number	Age Sex	BSA (M²)	Heart rate	Mean pressure (mm. Hg) PA	PCW or LA	RA
A Patients with atrial septal defect and pulmonary arterial pressures less than 25 mm. Hg						
1	24 F	1.41	78	16	7	7
2	32 F	1.60	109	17	10	5
3	12 M	1.02	85	8	2	0
4	62 F	1.78	73	24	10	9
5	35 M	04	80	18	11	9
6	27 F	1.75	85	14	7	6
7	18 F	1.54	75	16	6	6
8	15 M	2.00	86	20	10	9
9	33 F	1.59	101	18	6	4
10.	30 F	1.62	83	9	3	2
11	26 F	1.38	78	16	7	1
12	32 F	1.52	113	13	10	5
13	27 M	1.72	82	17	6	4
14	27 F	1.60	86	12	5	1
15	16 F	1.45	87	17	8	10
16	16 F	1.74	90	12	6	0
17	14 F	1.60	85	15	5	2
18	14 M	1.81	90	19	11	5
19	19 F	1.62	90	21	4	5
20	51 M	1.81	70	22	5	3
21	35 F	1.35	86	14	7	3
22	27 M	2.00	71	15	8	4
23	27 M	1.79	80	16	8	4
24	5 F	1.61	138	22	6	5
25	44 F	1.75	96	13	6	6
26	44 F	1.68	82	23	11	5
27	40 M	1.95	70	17	14	3
28	43 F	1.60	100	18	11	8
29	32 F	1.62	77	15	6	4
30	34 F	1.66	68	24	10	7
31	37 F	1.70	64	24	9	8
32	17 F	1.41	92	9	4	0
Mean	29.3	1.65	86	16.7	7.3	4.8
B Patients with atrial septal defects and pulmonary arterial pressures 25 mm. Hg or greater						
33	55 M	1.80	71	37	11	10
34	50 F	1.44	73	32	3	3
35	34 F	1.60	69	49	3	4
36.	44 F	1.52	66	40	7	4
37	37 F	1.38	90	78	14	5
38	21 F	1.42	99	39	7	5
39	32 F	1.63	80	60	4	4
Mean	39.0	1.54	79	47.8	7.6	4.7
C. Patients with atrial septal defect used for test in discriminant function analysis						
40	60 F	1.60	102	30	8	8
41	22 F	1.48	110	14	7	4
42	24 F	1.45	92	19	9	6
43.	31 F	1.64	80	17	8	5
44	15 F	1.41	133	16	5	2
45	19 F	1.60	98	13	6	3
46.	26 F	1.84	92	21	5	3
47	42 M	2.15	91	24	7	7

*Used in test series for discriminant analyses.
BSA: Body surface area in square meters; *PA*: Mean pulmonary arterial pressure; *PCW*: Mean pulmonary wedge pressure; *LA*: Mean ... *PBF*: Pulmonary blood flow; *SBF*: Systemic blood flow.

Blood flow index (L/m /M²)		PVR (dynes cm⁻⁵ sec)	Stroke index (c.c./beat/M²)		Arterial saturation (%)	PBF/SBF
Pulmonary	Systemic		RV	LV		
12 69	2 96	40	163	38	98	4 3
9 80	4 23	46	90	39	98	2 3
32 20	6 88	16	379	81	94	4 7
5 57	2 32	113	74	31	89	2 4
3 26	2 31	84	41	29	90	1 4
6 71	3 27	48	79	38	98	2 1
7 23	2 49	72	96	33	100	9
6 34	3 44	5⁻	74	40	97	1 8
21 57	3 45	28	214	34	96	6 3
8 79	3 51	34	106	42	9	2 5
7 40	2 45	70	95	31	97	3 0
13 98	3 55	11	124	31	9	3 9
9 48	3 63	50	116	44	95	2 6
13 87	2 54	24	161	30	94	5 5
7 13	3 00	70	82	34	96	2 4
5 41	2 40	41	60	27	94	2 3
6 07	2 10	80	71	_5	9⁻	2 9
13 20	3 81	26	147	42	97	3 5
4 32	2 97	191	48	33	86	1 5
5 84	2 67	128	83	38	94	2 2
11 23	3 10	37	131	36	95	3 6
10 63	3 85	26	150	54	95	2 8
11 93	3 63	28	149	45	95	3 3
19 12	3 42	42	139	25	97	5 6
5 79	1 11	55	60	12	100	5 2
5 93	2 44	96	72	28	9	2 5
6 32	2 11	19	90	30	94	3 0
7 72	2 51	46	77	25	94	3 1
7 96	2 07	56	103	27	97	3 8
12 50	2 93	54	184	43	9⁻	4 3
9 81	3 37	72	153	53	94	2 9
6 26	2 98	46	68	32	97	2 1
9 88	3 04	56 1	115	36 0		3 2
2 90	2 17	398	41	31	89	1 3
4 19	2 61	358	56	35	90	1 6
4 77	2 70	457	69	39	90	1 8
4 78	2 12	369	72	33	95	2 3
5 34	1 71	694	59	19	91	3 1
6 40	1 96	18_	65	20	97	3 3
6 85	3 50	40	86	47	95	2 0
5 04	2 40	4_3	64	31 9		2 2
6 51	3 42	169	64	34	86	1 9
7 44	4 16	51	68	38	95	1 8
26 33	3 12	21	28⁻	34	95	8 4
7 08	1 9	62	85	24	99	3 7
6 04	3 63	128	49	30	94	1 7
13 46	3 36	24	149	4	91	5
10 07	2 88	69	109	31	96	3 5
5 52	3 09	110	61	34	85	1 8

left atrial pressure RA Mean right atrial pressure PVR Pulmonary vascular resistance RV Right ventricle LV Left ventricle.

for 3 minutes and analyzed by the Scholander method for oxygen and carbon dioxide content Calculations of pulmonary and systemic blood flow and the size of the shunts were made by standard formulae[1] The oxygen content of mixed venous blood was assumed to equal the oxygen content of the average of inferior and superior vena caval blood Pulmonary venous blood was assumed to be 95 per cent saturated unless direct measurements of pulmonary venous blood or arterial blood indicated a higher saturation than this in which case the higher value was used for calculations

The apparatus used to record the kinetocardiograms consists of a metal bellows connected by means of a stiff plastic tubing to a P5A Statham strain-gauge transducer[2,3] Attached to the bellows is a metal probe which can be placed perpendicular to the chest wall at any point desired The entire bellows assembly is mounted on a crossbar above the patient in order to elicit an absolute low frequency displacement movements of the chest wall rather than relative interspace motion as sensed with the apexcardiographic technique The kinetocardiographic technique is essentially linear for low frequency movements (0 to 20 cycles per second) There is a resonance peak at 80 cycles per second but this is well out of the frequency recording range of the movements encountered over the precordium In addition there is no phase shift in the frequency range being studied The records are reproducible day to day in the same subject with insignificant alteration in amplitude or contour as long as the recording technique is kept constant.[4] The traces in the study were recorded on an Electronics for Medicine DR-8 oscillograph or on a Sanborn four-channel direct writer Records were usually obtained from precordial positions corresponding to the electrocardiographic V leads These are designated as K_{14}, K_{24}, K_{44}, etc The first subscript corresponds to the head foot vertical location of the V lead and the second subscript to the intercostal space Thus K_{14} is the kinetocardiographic trace just to the right of the sternum in the fourth intercostal space and K_{24} is located to the left of the sternum in the fourth intercostal space Computer analysis of only the K_{14}, K_{24} and K_{44} records was undertaken in this study

The kinetocardiographic records were digitized using a Gerber digital data reduction system the output of which is fed directly into an IBM 026 punch card unit. Thus, the amplitude of the kinetocardiographic complex was converted into digital values with an accuracy of three significant figures. A sampling rate of 0 0102 second was used. Two to three cycles were digitized from each record The kinetocardiographic records were normalized in length as well

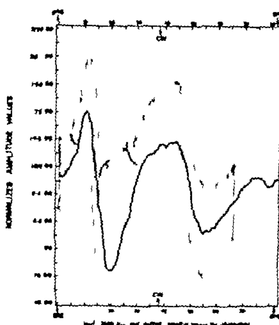


Fig *1* The mean kinetocardiographic complex (K position—V) from patients with atrial septal defects and mean pulmonary arterial pressure below 25 mm Hg The heavy line represents the mean complex and the shaded area represents one standard deviation about the mean. The arrows labeled *QRS* mark the onset of the QRS complex of the electrocardiogram and the arrows at the end mark the end of one complex. The arrow marked *CIN* represent the carotid incisural notch or the end of systole The amplitude values are normalized digital values. The number on the X-axis represents the number of digital points (83), which are approximately 10 milliseconds apart. The curved arrow labeled *1* points to the initial outward ventricular movement which is probably due to right ventricular activity This is exaggerated over normal in amplitude and duration. The curved arrow labeled *2* points to the marked inward movement associated with ejection presumably due to changes in stroke volume Arrow *3* points to the fused mid and late outward systolic movements.

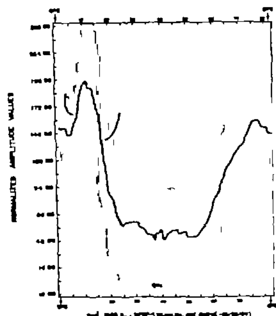


Fig. 2. The mean complex from the K_{44} position (corresponding to the V_4 position) in patients with mean pulmonary arterial pressures less than 25 mm. Hg. The heavy line represents the mean complex, and the shaded area represents one standard deviation about the mean. (See Fig. 1 for information concerning the coordinates.) The curved arrow *1* points to the initial outward ventricular movement, which presumably is due to right ventricular activity. The curved arrow *2* points to the systolic retraction which occurs during the ejection, and it is markedly pronounced in these patients with mean pulmonary arterial pressures less than 25 mm. Hg.

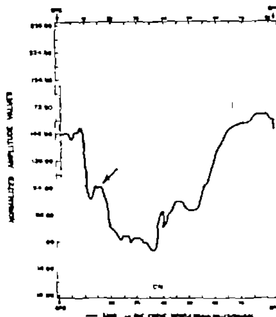


Fig. 3. The K_{43} trace (V_3 electrocardiographic position) in patients with mean pulmonary arterial pressures less than 25 mm. Hg. The heavy line represents the mean complex, and the shaded area represents one standard deviation about the mean. The coordinates are the same as those in Fig. 1.

as in amplitude. The normalization in amplitude was considered to be necessary in order to minimize (1) differences in amplitude in the records due to variations in the thickness of the chest wall* and (2) variations in recording sensitivity of the apparatus. This was accomplished by dividing each digital amplitude throughout the cycle by the mean area under the curve. This procedure was chosen to minimize the above-mentioned two variables while still retaining variations in amplitude due to heart disease. After this procedure the complexes were normalized in length so that each point in the complex could be compared to the same point in a different patient. All complexes were expanded or contracted to a cycle length of 0.83 second (systole and diastole were handled separately.) Interpolation of amplitudes was made should the new point fall between two original points. The records were then divided into two groups: (1) those in which the pulmonary arterial pressures were less than *25* mm. Hg and (2) those in which the pressures were 25 mm. Hg or greater. Each group was processed separately (Table I, *A* and *B*). An over-all mean complex for each kinetocardiographic position was obtained along with the standard deviations at each point along the curve.

Discriminant analyses[7, 8] were performed on the records from 38 of the initial 39 patients. (One was omitted by oversight.) After the analyses were made, 8 additional patients who were catheterized after the initial collection of data, and the one previously omitted, were used to test the discriminate function as determined on the

*Normal thin people have larger precordial movements than normal obese people, whereas the contours of the records are similar.

A more detailed description of the procedures for normalizing the records is in preparation and can be obtained directly from the authors.

first 38 patients. The procedure was performed using various amplitude values in the kinetocardiogram as variables, choosing initially every fourth point for a total of 19 points throughout the cardiac cycle. The best points were selected from the K_{11}, K_{31} and K_{41} records for final discriminate analysis. Five points of kinetocardiographic amplitudes were employed from the K_{11} trace, 11 points from the K_{31} trace, and 4 points from the K_{41} trace. Analyses were performed on IBM 1620 and 7040 computers.

Hemodynamic findings

Studies on 47 patients form the basis of this report. The relevant hemodynamic data are presented in Table I, A, B and C. Using a mean pulmonary arterial pressure of 25 mm. Hg as the upper limit of normal,[2,1] 39 were normotensive and 8 (17 per cent) were hypertensive. This is in agreement with the observations of others: Storstein and Efskind,[11] 12 per cent; Bestterman,[12] 16 per cent; and Rowe and associates,[13] 21 per cent. In the group with normal mean pulmonary arterial pressures there was a great variation in the pulmonary blood flow; however, the systemic blood flow was normal in all but 5 patients (below 2.2 L. min. M.²). The calculated pulmonary vascular resistance was less than 200 dynes sec. cm.$^{-5}$ in all cases in the low pressure group. There was much less variation in the pulmonary blood flow in the hypertensive group. Four of these 8 patients had abnormally low systemic blood flows. With one exception, the calculated pulmonary vascular resistance was greater than 200 dynes sec. cm.$^{-5}$ in this group.

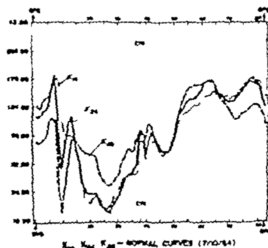


Fig. 4. Superimposed normal K_{11}, K_{31}, and K_{41} traces for comparison with the abnormal records.

Mean curves

Figs. 1, 2 and 3 present the mean complex of the K_{11}, K_{31} and K_{41} records from patients with mean pulmonary arterial pressures below 25 mm. Hg. Fig. 4 is a schematic diagram of normal curves for comparison. The middle line in Figs. 1, 2, and 3 represents the over-all mean complex; the lines above and below represent one standard deviation above the mean as calculated for each digital value along the curve. The following points are worthy of note. (1) The right ventricular movement as noted for the mean curve is prominent and sustained over normal (*first curved arrow*) in the K_{11} and K_{31} records. (2) The chief movement during ejection systole is inward (systolic retraction movement) (*second curved arrow*). (3) There is a slow mid systolic outward movement in the K_{31} trace, reaching a peak about the end of ejection systole, instead of two more widely separated movements such as occur in normal subjects (*third curved arrow*). (4) The left ventricular thrust is very small in the K_{41} trace (*diagonal arrow*).

Figs. 5, 6 and 7 present not only the mean curves as described above, but in addition have superimposed for comparison the mean complex and standard deviations for the patients who have elevated mean pulmonary arterial pressures of 25 mm. Hg or greater. Although the differences are apparent, the most obvious change in the records of patients with elevated mean pulmonary arterial pressures is the decreased inward movement during systole and the appearance of a large, outward mid systolic movement (*diagonal arrow in the K_{31} record*). Thus, it becomes apparent that the contour of the records from these patients depends upon the intracardiac hemodynamics.

Discriminate analysis

Discriminate analysis is a mathematical approach used to maximize differences

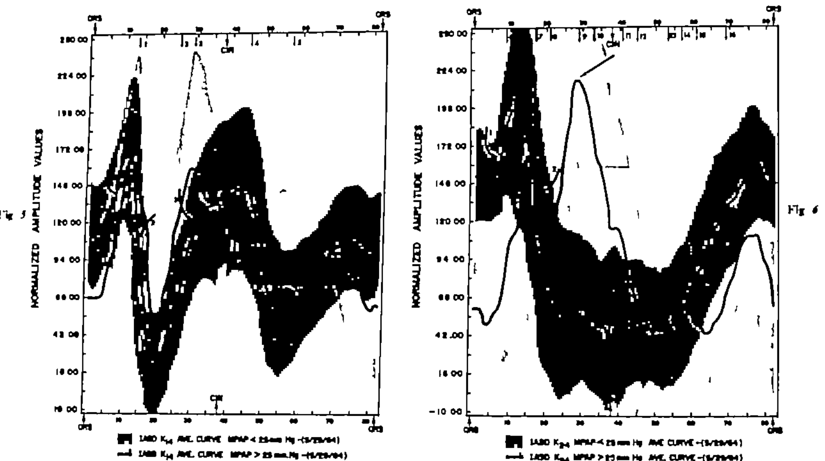


Fig 5 A overlay of the mean curves and stand ird deviations from patients with mean pulmonary arterial pressures below and above 25 mm Hg The dark shaded areas represent the part the two K traces wh h erlap Note that no complete separation occurs between the two urves at any point; however the configura t on of the urves ary The vert l rrow at the top labeled *1 2 3 4* and *5* represent points that were selected in the discriminate analysis.

Fig 6 The mean urves nd standard deviation from patients with mean pulmonary arterial pressures both less and greater than 25 mm Hg The dark shaded are g in represent the point in the two groups which overlap Note that the records taken from this position (K_{24}) have two major area of complete separation one n the i ltial ventricula portion nd the second during mid-systole. The contour of the record from patients with elevated pulmonary arterial pressures is predom nately outw rd mid-systolic movement (*indicated by the diagonal arrow*), whereas the movement during ejection in patients with pulmonary arterial pressures less than 25 mm Hg is n nward movement a indicated by the curved arrow labled *2* The numbered vertical arrows at the top represent the points that were selected for use in the discriminate analysis.

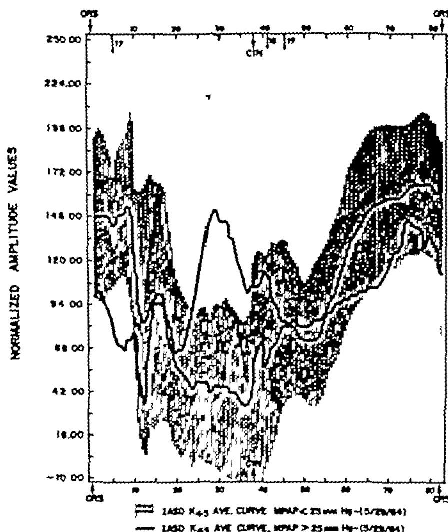


Fig. 7. An overlay of the mean and standard deviations on the curves taken from the K_{45} (V) position in patients with mean pulmonary arterial pressures less and greater than 25 mm. Hg. Note the marked difference in contours of the mean curves. Although the curves are quite different, there is some overlap in the curves throughout the whole complex. The vertical arrows numbered *18* and *19* represent those points chosen for discriminate analysis.

between two or more sets of data.[7,8] Weight values are obtained for each of the variables and from these a discriminate number can be calculated from the following formula

$$Z = \sum_{i=1}^{N} B_i X_i$$

B_i is the weight factor determined by discriminate analysis, X_i is the amplitude of the kinetocardiogram at position i and N is the number of positions in the cycle used for analyses. The symbol Σ is the sum of the products. Through error in selection only 38 of the patients in the first group as described were included in the initial analysis. Later the excluded patient and 7 new ones (catheterized since the data were initially collected for study) were added in order to test the discrimination as previously determined.

Fig. 8 presents a plot of the discriminate numbers using 19, 12, and 7 variables. The x and o symbols indicate the patients used initially to determine the weight factors, and the other symbols (*solid circles and crossed open circles*) the pa-

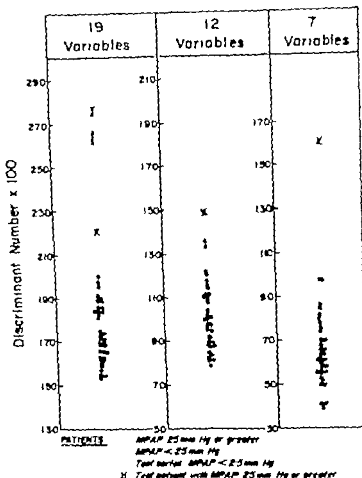


Fig. 8. Plot of the discriminate numbers calculated from the weight values obtained from discriminate analysis. The x and o symbols represent those patients used in determining the discriminant function with both mean pulmonary arterial pressures less than and greater than 25 mm. Hg, respectively. The solid circles and the crossed open circles represent those additional patients used to test the discriminate analysis. Notice that in all instances there is no overlap between the two groups of patients. Thus it is possible using 19, 12, or 7 variables to divide the patients with atrial septal defects into two groups: those with mean pulmonary arterial pressures greater than 25 mm. Hg and those with mean pulmonary arterial pressures less than 25 mm. Hg.

tients used to test the system. Table II presents the weight factors for each patient and the significant figures. Note from Fig. 6 the wide separation between the patients with elevated mean pulmonary arterial pressures and those with normal pressures in all three instances. From observation of Fig. 8 it is apparent that the best discriminant number between the two groups of patients is 210 using 19 variables, about 143 using 12 variables, and about 120 using 7 variables. Since all of these patients with elevated mean pulmonary arterial pressures had pulmonary vascular resistances of 200 dynes sec. cm.$^{-5}$ or greater (except one patient in the test series), the same discriminate function can be used to predict or detect increased pulmonary vascular resistance as well as elevated mean pulmonary arterial pressure.

The location within the cardiac cycle of the amplitudes from the kinetocardiograms which were selected by the discriminate analysis as the points of *most* importance is of some interest. The arrows (*straight or vertical*) at the top of Figs. 5, 6, and 7 indicate the 19 points. In most instances they correspond to the places on the two groups of curves which are *most* widely separated.

Table II. Weight factors for kinetocardiographic variables found by discriminant analysis

KCG variable	Using 19 variables	Using 12 variables	Using 7 variables
1	003030	003408	002877
2	0005654	—	—
3	001833	002603	002599
4	001305	001270	—
5	004933	006010	005996
6	001364	—	—
7	001151	—	—
8	− 001137	− 001279	− 001534
9	005988	004972	002761
10	− 002906	− 002568	—
11	0007826	—	—
12	003684	− 002028	—
13	− 001427	− 0006283	—
14	007891	—	—
15	− 005351	− 001778	− 002919
16	001657	—	—
17	0002734	—	—
18	001455	+ 001648	—
19	− 003607	− 004149	− 001995
	$r^2 =$ 93	$r^2 =$ 90	$r^2 =$ 85
	F ratio = 11 96	F ratio = 18 80	F ratio = 25 20

Comments

The genesis of kinetocardiographic patterns associated with heart disease is obviously complicated. It appears to be likely from previous studies[14, 15] that hypertrophy of the ventricles is an important factor in producing the abnormality encountered. However, the present study would indicate that intracardiac hemodynamics (pulmonary arterial pressure) apart from hypertrophy significantly affect the contour. Supporting this hypothesis are observations before and after mitral valvulotomy in patients with mitral stenosis. The records often change remarkably in countour within 10 days after the operation.[16] If the abnormality in precordial motion was due solely to hypertrophy, so rapid a change would not be expected. Other studies[17, 18] also support the concept that the intracardiac hemodynamics significantly influence the contour of the kinetocardiogram.

Thus, there are several points of interest which appear to warrant emphasis. (1) The contour of the kinetocardiographic records, or for that matter of any displacement precordial records including the apexcardiogram, cannot be fully interpreted or evaluated without taking into consideration cardiac function or intracardiac pressures and flow.* The configuration of precordial movements is not solely related to hypertrophy or specific anatomic lesions. (2) It does appear to be possible to predict or detect certain intracardiac hemodynamic changes (although now only gross estimates). Up to now these data were obtainable only by cardiac catheterization. Prediction should be improved by the use of faster sampling rates of a semiautomatic conversion system. Added accuracy also may be possible by using in the discriminant analysis other readily obtained clinical information. (3) From consideration of the variables selected (*see arrows in Figs. 5, 6, and 7*) one of the main distinguishing features between the two groups of patients is the presence of the large sustained mid-systolic outward movement in the K_{34} record instead of the inward movement which occurs in patients with normal pulmonary arterial pressures. Indeed, one can often detect this difference by palpation at the bedside.

*So far the prediction of pulmonary flow in these patients has been only moderately successful.

Summary and conclusions

1 The study consists of a computer analysis of the kinetocardiographic records in patients with uncomplicated secundum atrial septal defects.

2 Mean complexes and statistical limits have been presented for the kinetocardiographic traces taken from precordial locations corresponding to the V_1 V_3, and V_4 electrocardiographic positions.

3 It is possible through discriminate analysis to divide the patients with atrial septal defects into two groups (a) those with mean pulmonary arterial pressures below 25 mm Hg and (b) those with mean pulmonary arterial pressures of 25 mm Hg or greater

4. Patients with a pulmonary vascular resistance over 200 dynes sec. cm^{-5} can in most instances, also be separated from those with normal pulmonary vascular resistances

Fortran IV programs for the computer analyses performed in this paper are available from the authors.

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Hemodynamic and catecholamine changes during a standard cold pressor test

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The intriguing possibility that hemodynamic changes and levels of circulating catecholamines may be interrelated has been investigated on a number of occasions with generally negative results. In this laboratory earlier studies both at rest and during infusion of norepinephrine had failed to show any correlation between the two.[1] Despite these results, however, it was thought that some relationship might become apparent if studies were made before and during periods of acute circulatory stress. To produce the stress, the standard cold pressor test was employed.

Methods

The subjects were ambulatory males drawn from the general medical and surgical wards of a Veterans Administration hospital and consisted of 13 normal and 16 labile hypertensive patients, the latter selected in order to provide a wide range of hemodynamic variables.[2] Labile hypertension was defined as a blood pressure which was elevated on the day of admission to levels greater than 150/100 mm. Hg but which fell to normotensive levels at some time during the next 3 days without any medication or treatment of the patient other than that provided by standard hospital routine. Some of the patients in both the normal and labile hypertensive groups were studied on each of 2 successive days in order to provide some data on individual and group day-to-day variability in the hemodynamic and catecholamine responses to the cold pressor test.

All patients were studied fasting and

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supine, and in order to allay apprehension the test procedure was explained to the patient on the day preceding his study. Some patients received hypnotics on the evening preceding their study; none was receiving any other drugs. When the subject arrived in the test room a No. 18 Cournand needle was inserted under local anesthesia into the brachial artery of the right arm and an 8-inch large-bore polyethylene catheter was placed into an antecubital vein in the left arm and connected to a slow drip of 5 per cent dextrose in water. Auscultatory blood pressures (BP) were recorded upon arrival and periodically thereafter until stable. At this point samples of arterial blood for determination of catecholamines were drawn and the first cardiac output was measured. After 10 minutes of rest, during which pressures were recorded every 2 minutes, the subject's left hand was immersed to wrist level in water at 4°C. Blood pressures were recorded at 30 seconds and just prior to the second measurement of cardiac output during the second minute of immersion. Samples of blood for the determination of catecholamines were drawn between the two determinations of pressure.

In an attempt to minimize vagally mediated compensatory mechanisms of the responses to the cold pressor test, 7 normal and 8 labile hypertensive patients received 1.2 mg. of atropine intravenously after the control samples of blood for determination of catecholamines and the measurements of cardiac output had been obtained. In these subjects, the levels of catecholamines and the cardiac output were redetermined 8 minutes after atropinization and in an additional 8 minutes the cold pressor test was performed in the manner described above.

Cardiac output (CO) was determined by the indicator-dilution method utilizing radioiodinated human serum albumin as indicator and an interrupted sample technique. Samples were analyzed and the results were calculated in a standard manner.[3] This method in our laboratory has a coefficient of variation of the difference of 11 per cent for CO* and 12.5 per cent for total peripheral resistance (TPR) in labile hypertensive subjects studied 10 minutes apart.

The samples of blood for determination of catecholamines were placed immediately after collection in prechilled centrifuge tubes and delivered to the laboratory within 30 minutes. Catecholamines were determined by a modification similar to Cohen's,[3] of the trihydroxyindole method of Lund.[4] The determination consists of adsorbing the catecholamines onto alumina from plasma adjusted to pH 8.4. The alumina is then transferred to a chromatographic column and the catecholamines are eluted with 0.2 molar acetic acid. Then 0.6 c.c. of pH 6 buffer is added to an aliquot of this eluate in order to increase the fluorescence of epinephrine (E) and norepinephrine (NE) and to decrease that of other catecholamines which may be present. NE and E are then converted to noradrenochrome and adrenochrome, respectively, by oxidation with 0.1 c.c. of potassium ferricyanide. At this point, the addition of strong base isomerizes the catecholamines to their respective lutines, adrenolutine being formed immediately and noradrenolutine being formed in 4 to 6 minutes. Fluorescence was read in an Aminco Bowman spectrophotofluorimeter at an activating wave length of 405 mμ and fluorescent wave length of 490 mμ for norepinephrine and an activating wave length of 435 mμ and fluorescent wave length of 580 mμ for epinephrine. With the use of this technique, recoveries at concentrations of 10 to 20 μg per liter of plasma have been 93 ± 14 per cent for norepinephrine, and 92 ± 11 per cent for epinephrine. Calculations were made in the standard manner.

Results

The results are shown in Tables I-IV and in Figs. 1 and 2.

Table I shows the data obtained from 6 normal subjects, 5 of whom were studied twice, and Table II gives the results for 7 labile hypertensive patients, 2 of whom were also tested twice. The ages of the two groups are entirely comparable (normal subjects 39±5.6 years; labile hypertensive subjects 40±4.8 years). Mean CO and TPR for the group of normal subjects

$$\text{*Coefficient of variation} = \frac{\text{Standard deviation of pair differences} \times 100}{\text{Mean C.O.}}$$

Table I Hemodynamic and catecholamine changes during the cold pressor test in normal subjects

Name	Control values					
	BP	Pulse	CO (L/min)	TPR (dynes sec. cm⁻⁵)	Arterial NE (µg/L. plasma)	Arterial E (µg/L. plasma)
J H	100/58	66	6 98	814	0 76	0 24
V V	132/84	104	8 40	952	0 96	0 37
V V	134/85	100	9 14	902	1 24	0
H H	122/70	76	8 65	766	0 18	0
H H	110/65	74	8 00	800	0	0
G G	134/80	93	10 32	776	0	0
G G	126/84	72	6 83	1 148	0 78	2 88
A P	104/72	88	7 24	914	0	0
A P	110/70	96	8 10	840	0	0
A L	124/77	80	10 90	738	0 78	0
A L	120/70	80	9 14	780	0 18	0
Mean	120/74	84	8 52	857	0 44	0 32
S D	±12/9	±12	±1 3	±118	±0 46	±0 57

Table II Hemodynamic and catecholamine changes during the cold pressor test in labile hyper

Name	Control values					
	BP	Pulse	CO (L/min)	TPR (dynes sec cm⁻⁵)	Arterial NE (µg/L. plasma)	Arterial E (µg/L. plasma)
W B.	144/104	64	5 83	1 683	1 00	0
M L.	148/78	80	13 66	590	0	0
M L	140/78	88	10 92	730	0	0
E C	136/84	82	11 50	660	0	0
E C	138/80	96	11 00	750	0	0
J F	124/84	80	10 48	786	0	0
M D	150/88	84	9 76	862	0 38	0
T H	148/97	84	7 04	1 295	0 41	0
R W	125/75	84	7 90	932	0 37	0
Mean	138/85	82	9 79	921	0 24	0
S.D	±11/10	±8	±2 4	±324	±0 34	–

were 8.52 L. per minute and 857 dynes sec cm⁻⁵ the corresponding values for the labile hypertensive subjects were 9 78 L. per minute and 920 dynes sec cm⁻⁵

The most common hemodynamic response to the cold pressor test consisted of an increase in BP and TPR and a fall in CO. This was seen in 6 of 11 observations on normal subjects and in 4 of 9 observations on labile hypertensive subjects. In individuals who did not show this pattern varying combinations of changes in BP CO and TPR occurred and the largest increases in TPR were not necessarily as-

Changes during cold immersion					
BP	Pulse	CO	TPR	Arterial NE	Arterial E
+20/+14	− 6	−0 27	+211	+0 38	+0 51
+12/+ 6	− 4	−0 85	+193	−0 28	−0 14
+ 6/+ 7	0	+0 24	+ 78	+0 52	0
+15/+ 8	0	−0 42	+186	+0 23	0
+18/+11	+ 8	−0 37	+199	+1 09	0
+10/+20	− 7	−0 42	+154	0	0
− 1/+ 6	+ 2	+1 31	−148	−0 10	+0 60
− 4/− 8	+ 6	−0 63	+ 30	0	0
+10/+10	0	−0 97	+136	0	0
+20/+16	+14	+0 88	− 12	+0 82	+0 18
+28/+20	0	+0 18	+ 70	+0 44	0
+12/+10 ± 9/7	+ 1 ± 6	−0 12 ±0 67	+100 ±111	+0 28 ±0 42	+0 10 ±0 23

tensive subjects

Changes during cold immersion					
BP	Pulse	CO	TPR	Arterial NE	Arterial E
−26/−16	+20	−0 28	−135	+0 77	0
+ 6/+15	+ 4	−0 65	+ 74	+0 3	0
+17/+16	+ 4	+3 68	−139	+0 18	0
+20/+10	+ 6	−1 9	+340	0	0
− 4/0	−16	−0 4	− 50	0	0
+36/+34	+ 4	+1 12	− 7	0	0
+10/+ 2	− 4	−0 58	+165	−0 38	+1 4
+22/+ 9	+ 4	+0 80	+ 11	−0 41	0
+ 5/+ 5	0	−1 77	+333	0	0
+10/+ 8 ±18/14	+ 2 ± 9	0 ±1 7	+ 65 ±181	+0 06 ±0 36	+0 14 ±0 41

sociated with large pressor responses In 4 patients notably M.L. (day 2) and J F (Table II) pressor responses were accounted for solely by increases in cardiac output and resistance remained constant or actually fell Both the base-line hemodynamics and the cold pressor response were more variable in labile hypertensive patients than they were in normal subjects.

Five normal and 2 labile hypertensive patients were studied on each of 2 successive days. One patient from each group gave a "Hyperreactor" response (

Table III. Hemodynamic and catecholamine changes in atropinized normal subjects during the

Name	Postatropine levels					
	BP	Pulse	CO (L./min.)	TPR (dynes sec. cm.⁻⁵)	Arterial NE (µg/L. plasma)	Arterial E (µg/L. plasma)
A.P.	113/70	124	9.94	684	0	0
S.O.	138/84	96	7.84	1,040	—	—
L.G.	152/104	118	11.30	835	0	0.82
H.B.	120/74	100	8.10	912	—	—
T.O.	118/80	108	8.21	933	0.27	0
C.M.	120/80	120	8.86	840	0.27	0
J.J.	130/84	108	7.10	1,115	—	—
Mean	127/82	111	8.76	914	0.14	0.21
S.D.	±14/11	±11	±1.43	±141	±0.16	±0.41

Table IV. Hemodynamic and catecholamine changes in atropinized labile hypertensive subjects

Name	Postatropine levels					
	BP	Pulse	CO (L./min.)	TPR (dynes sec. cm.⁻⁵)	Arterial NE (µg/L. plasma)	Arterial E (µg/L. plasma)
W.I.	144/92	92	9.06	996	0	0.68
P.S.	128/84	100	7.40	1,050	0	0
C.K.	160/98	80	4.50	2,080	0	0
H.W.	138/93	120	4.86	1,861	0.18	0.27
F.S.	128/90	96	8.80	936	0	0
P.I.	138/95	100	7.92	1,060	0.18	0
A.H.	140/93	104	9.60	928	0	0.71
N.I.	130/85	100	7.70	976	0.68	0
Mean	138/92	99	7.48	1,236	0.13	0.21
S.D.	±11/5	±11	±1.88	±449	±0.24	±0.32

crease of at least 20 mm. Hg systolic and/or 15 mm. Hg diastolic)[8] on one day and not on the other. Even when the pressor response on the 2 days was similar, the hemodynamic mechanism through which the changes in pressure occurred might vary.

Patients A.P. (day 1), E.C. (day 2), and W.B. were remarkable in that the BP fell during the cold pressor test. Similar responses have been described previously without adequate explanation.[6] There is nothing in the pretest hemodynamic or catecholamine set or in the cold pressor catecholamine response in the present study which can serve to distinguish these individuals from their more conventionally reacting fellows.

In Fig. 1, changes in arterial NE during cold immersion are plotted against the corresponding changes in TPR. Arterial blood was used because it mirrors mixed venous catecholamines more accurately than does blood from a peripheral vein

cold pressor test

Changes during cold pressor					
BP	Pulse	CO	TPR	Arterial NE	Arterial E
−5/−14	0	+1 76	−158	+0 60	+0 23
+16/+6	0	−0 80	+244	—	—
+18/+8	+8	−2 85	+440	0	−0 41
+10/+6	−4	−0 80	+260	—	—
+12/+10	0	−1 11	+195	+0 41	0
+15/+10	−4	−0 34	+145	+0 28	0
+20/+16	+10	+0 18	+181	—	—
+12/+6	+1	−0 57	+187	+0 32	−0 05
± 8/9	± 5	±1 41	±179	±0 25	±0 27

during the cold pressor test

Changes during cold pressor					
BP	Pulse	CO	TPR	Arterial NE	Arterial E
+16/+18	+8	+0 88	+14	0	−0 18
+26/+28	0	+1 3	+100	0	+0 18
+30/+20	+8	+3 0	−570	0	+0 86
+26/+45	0	+1 16	+109	−0 08	+0 74
+12/+25	+4	+0 3	+207	+0 78	0
+32/+15	0	+1 28	+70	+0 19	0
+10/+5	+8	−0 84	+154	+0 09	+0 43
+15/+20	0	−0 20	+272	+0 37	0
+21/+22	+4	+0 86	+45	+0 17	+0 25
± 9/12	±4	±1 16	±261	±0 28	±0 37

In 6 of 11 observations on normal subjects the changes in resistance and catecholamines were in the same direction and in only one subject was a rise in resistance accompanied by a fall in NE. In 4 of 9 observations on the labile hypertensive group divergent resistance-catecholamine changes were recorded and in only one instance were the changes directionally parallel In both groups, significant changes in resistance could occur in the absence of change in catecholamines, and the converse was also true Seven individuals showed no measurable changes in catecholamines during the cold pressor test in 6 of these the values remained at zero throughout the study

In view of the variability of the hemodynamic response in our initial group of subjects, it was decided to atropinize new groups of patients in order to determine whether the minimizing of vagally mediated compensatory mechanisms would reduce the hemodynamic variability or af

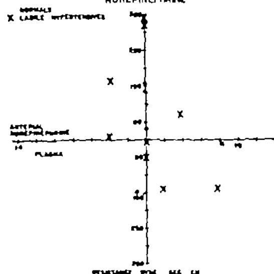


Fig. 1. Scatterplot of the change in arterial norepinephrine concentration vs. the change in total peripheral resistance during the cold pressor test in normal and labile hypertensive subjects.

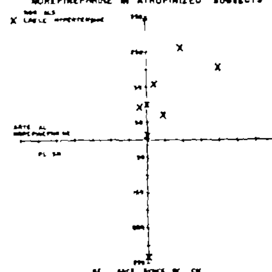


Fig. 2. Scatterplot of the change in arterial norepinephrine concentration vs. the change in total peripheral resistance during the cold pressor test in normal and labile hypertensive subjects given 1.2 mg. of atropine intravenously. The greatest increase in TPR in a normal patient was +440 dynes sec. cm.$^{-5}$; the greatest decrease in TPR in a hypertensive patient was −370 dynes sec. cm.$^{-5}$. These were plotted at the extremes of the graph rather than at their precise locations, thus permitting the scale to be unchanged from Fig. 1.

fect the hemodynamic-catecholamine correlation.

In 7 normal subjects, 1.2 mg. of atropine given intravenously produced a mean increase in pulse rate of 31 per minute and in 5 of the 7 some increase in CO and BP. Mean values for the entire group were: BP, +6/+9; CO, +0.66 L. per minute; TPR, +13 dynes sec. cm.$^{-5}$. And in 4 subjects in whom blood catecholamines were determined, both arterial NE and arterial E were zero. The corresponding changes after atropinization of 8 labile hypertensive subjects were: BP, −1/+6; CO, −0.57 L. per minute; pulse, +28 per minute; TPR, +153 dynes sec. cm.$^{-5}$; arterial NE, −0.04 μg per liter; arterial E, +0.05 μg per liter.

Tables III and IV show the hemodynamic and catecholamine changes which occurred during the cold pressor test in the atropinized normal and labile hypertensive subjects. The response of normal patients was not appreciably different from that of their unatropinized counterparts. In 6 of 7 subjects BP and TPR increased and in 5 of these 6 the CO fell. In 2 instances the pulse rate fell during the cold pressor test, which suggests that either reflex vagal stimulation was sufficiently intense to overcome the atropine block or there was reflex reduction in sympathetic tone or both.

In each of the 8 labile hypertensive patients who were given atropine, BP increased during the cold pressor test. TPR increased in 7 of 8 instances and CO increased in 6 cases and decreased in 2. This uniformity in hemodynamic response, although also seen in the atropinized normal group, stands in particular contrast to the diversity of hemodynamic changes seen in the unatropinized labile hypertensive group.

The changes in catecholamines were similar in magnitude and direction in atropinized and unatropinized patients of both groups. In Fig. 2 it can be seen that the hemodynamic and catecholamine changes in the atropinized labile hypertensive patients tended to be in the same direction, making this group resemble the normal group in this regard. The resemblance is due more to the atropine-induced reduction in the variability of the hemodynamic response of the labile hyperten-

sive patients to cold than it is to any effect of atropine on catecholamines

Changes in arterial epinephrine are not shown graphically. Inspection of the tables will indicate that neither resting levels of epinephrine nor changes in epinephrine during the cold pressor test correlated with any hemodynamic parameter.

Discussion

It has long been hoped that the development of sufficiently specific and sensitive methods for measuring catecholamines would help define the relationship between autonomic activity and its cardiovascular concomitants.

At the present time two principal methods of chemical quantitation of catecholamines are available. These are, with their modifications, the trihydroxyindole method of Lund[6] and the ethylenediamine method of Weil-Malherbe and Bone.[7] Neither method is ideal; the advantage of increased specificity with the trihydroxyindole method must be weighed against the greater sensitivity provided by the ethylenediamine technique. The more specific method was used in these studies, but nevertheless, it must be admitted that indisputable proof of the biologic activity of the measured compounds is lacking.

Several individuals showed no measurable change in catecholamines during the cold pressor test. These subjects make statistical analysis of the hemodynamic-catecholamine relationship difficult but do not necessarily preclude the presence of such a relationship, since it is entirely probable that greater methodologic sensitivity would permit identification of catecholamines in some of these patients. It is, of course, possible that circulating catecholamines were actually zero. Even in this instance, however, it is possible that changes in catecholamines occurred which were not reflected in circulating levels, since these represent an integrated expression of catecholamine release, tissue extraction, and metabolic transformation.

In the course of other studies we have previously noted that in labile hypertensive subjects, TPR and arterial NE over a 10-minute period tended to rise or fall with equal frequency.[1] In our present study, measurable changes in catecholamines during cold immersion occurred in 21 instances. In 16 of these arterial levels of NE increased. This observation suggests that an increase in NE may form part of the response to the cold pressor test. In the 16 studies during which arterial NE increased, TPR increased in 12 and decreased in 4. The two parameters could not be directly correlated.

Although this study was not intended to be primarily an investigation of the hemodynamic mechanisms underlying the cold pressor response, it was of interest to note that identical pressor responses may be achieved by varying combinations of change in CO and TPR. Similar observations on the cold pressor test have been made by Boyer[4] and for the stress imposed by mental arithmetic by Brod and associates.[8] The circumstances under which our tests were carried out are not those specified by its originators.[10] Despite this, accumulating evidence makes increasingly untenable the assumption that increases in BP may be equated with vasoconstriction.[14] These observations do not, however, necessarily deny significance to the pressor response itself.

Summary and conclusions

It has been shown that positive responses to cold pressor tests may occur on the basis of increases in total peripheral resistance, increases in cardiac output, or combinations of both, and that as a consequence of this hemodynamic interplay there was no correlation between the magnitudes of the pressor response and the change in resistance.

All hemodynamic parameters were more variable in labile hypertensive patients than in normal subjects.

A considerable number of patients in all groups studied showed no measurable change in catecholamines during the cold pressor test; however, arterial norepinephrine did increase in about half of the subjects studied and showed some tendency to directionally parallel the changes in total peripheral resistance in normal subjects but not in labile hypertensive subjects.

Atropinization tended to increase the blood pressure in both groups of st this increase was nc At

increases in cardiac output in normal subjects, and by increases in total peripheral resistance in labile hypertensive subjects. In this latter group atropine reduced the variability of the hemodynamic response to cold and since catecholamines were unaffected tended to make the hemodynamic-catecholamine relationship more directional

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Quantitation of QRS and ST segment responses to exercise

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Depression of the ST segment in the electrocardiogram recorded after moderate exercise is predictive of coronary occlusive disease.[1] Mattingly reported that 10-year follow-up of 145 patients who exhibited this ischemic response on a double Master two-step test revealed a cumulative 38 per cent incidence of myocardial infarction with a 55 per cent case fatality rate. Robb and Marks[2] found that the mortality rate from coronary heart disease ranged from 9 to 114 per 1,000 person years of observation as S-T segment depression increased from less than 1 to over 2 mm. in life insurance applicants who were tested by the same procedure. Rumball and Acheson[3] found a 29 per cent incidence of clinical coronary disease 4 to 7 years after strenuous exercise of 37 normal men of 40 to 54 years of age who showed ST segment depression. Recently, Doan, Peterson, Blackmon and Bruce[4] reported progressive increments in age-specific prevalence rates for postexertional segmental ST depression with advancing age in healthy middle-aged men who were exercised maximally. Only 2 of 201 clinically normal men tested by the double Master two-step test showed this response, whereas 18 exhibited it when stressed by a multistage maximal exercise test. Although it is likely that ischemic ST segment depression might be detected during submaximal exercise, the variations imposed by marked respiratory effort and bodily movement make ECG interpretation difficult, if not impossible.

If exertional and respiratory distortions in the exercise ECG are considered to be random events in relation to the heart cycle, their effects may be minimized substantially by the use of currently available computer averaging techniques. After preparation of a representative ECG sample for each period of observation, differences in ECG voltages can be analyzed quantitatively. Rautaharju and Blackburn[5] utilized this principle for reducing the random noise of exercise electrocardiograms. The ECG was recorded on a magnetic tape and the distance between record and play

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back heads was utilized to separate a triggering function (for the oscilloscopic sweep of the computer memory) by means of the R wave which was read by the record head and the analysis function of sampling the analog data as it subsequently arrived at the playback head These investigators scanned* ECG complexes for 0.5 second and limited averaging to 16 consecutive QRST complexes, thereby minimizing the averaging capability of the computer Smoothing and coincidence-logic triggering circuits were employed also but not described in detail

Material

Seventy three male faculty members who volunteered to participate in a prevalence study were selected but complete data for all workloads were preserved on only 57 subjects. Although all subjects were otherwise clinically normal they were classified by visual inspection of the conventional scalar tracings into 39 normal 9 borderline, and 9 abnormal *postexercise ECG* responses to maximal exertion according to criteria described previously

Methods and purpose

Details of clinical examination ancillary tests exercise testing ECG monitoring and criteria for ECG interpretation of postexercise responses were described previously [4] During these exercise tests, however the subjects did not hold the hand bar for guidance or support while on the treadmill The output from a Sanborn 100 electrocardiograph was recorded on two tracks of magnetic tape by means of a Mnemotron analog data recorder (Fig 1*A*) The ECG action potentials were not recorded simultaneously on both tracks but were separated by a constant interval determined by the physical distance between the record and playback heads and the tape transport speed When the latter was operated at 7½ inches per second the delay constant for re-recording on track 2 was 140 milliseconds The action potential underwent pulse frequency modulation prior to recording on track 1 When perceived by playback head track 1 it was demodulated amplified remodulated and directed to the record head of track 2 which was located immediately below the record head of track 1 The playback heads for both tracks were aligned vertically (Fig 1*B*) The high voltage R wave on track 1 was modified to trigger the computer which scanned and stored the identical but delayed wave-form data recorded on track 2 This arrangement assured computer storage of the PQ interval preceding the *same* electrocardiographic QRS complex which served as the trigger without this, only the ST and *subsequent* PQRS complexes of the following heart cycle would be stored Because of physiologic variations in the diastolic intervals with tachycardia, establishment of a theoretical isoelectric base line from which to measure ST segment shifts necessitated use of PQ rather than TP intervals.

The Mnemotron analog data recorder was a 3-speed 2 track recorder which utilized ¼-inch wide magnetic tape. With a tape transport speed of 7½ inches per second the frequency modulations had a linearity of ±0 2 per cent of full-scale voltage.

An Epsco Model DA 102 differential amplifier and Tektronix Type 162 waveform generator with Type 160 power supply were used to amplify and generate a square wave form from each signal on track 1 to trigger the oscilloscopic sweep of the computer for each signal on track 2

The Mnemotron computer of average transients (CAT) was a special-purpose binary-coded decimal digital computer with 400 addresses in a ferrite-core memory matrix which averages the analog voltages for *each* address, and summates all voltages for consecutive PQRST complexes cumulatively A Mnemotron Model 562 sweep counter is preset to 100 ECG complexes. The summated 100 voltages at each address are finally displayed as a single analog composed of 400 consecutive addresses. The summated voltages for all addresses may be displayed as a simulated analog of 400 consecutive voltages on a 3-inch oscilloscope or graphed on the conventional paper tape of an electrocardiograph. They may also be printed (on folded paper tape) in digital format on a scale

*Fig. 2 of Rautaharju and Blackburn's report shows the P wave for the subsequent, rather than the same, QRST complex, whereas Fig. 3 indicates that the amplified segment of ST begins with the downslope of R.

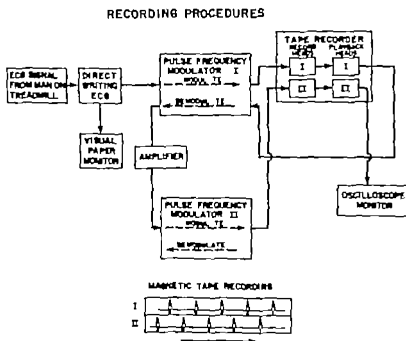


Fig. 1A See text.

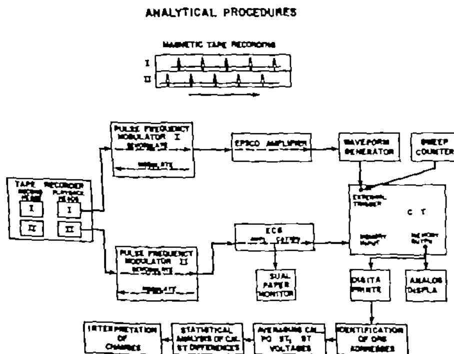


Fig. 1B See text.

ranging from 0 to 9.999 voltage units at a rate of 5 addresses per second by means of a Technical Measurement Company Model 500 printer. Both types of display may be read out of the computer simultaneously in a single operation.

ECG criteria for clinical classification by visual inspection

The postexertional ECG responses were used to classify the subjects into one of three categories in relation to myocardial ischemia: (1) *Normal response* not indicative of ischemia when ST junction and segment exhibited less than 1 mm (0.1 mv.) depression with consecutive heartbeats. (2) *Borderline response* possibly but not definitively indicative of mild ischemia when ST junction was depressed at least 1.5 mm (0.15 mv.) with every heartbeat and/or there was marked respiratory variation of ST segment depression of variable degree from beat to beat. (3) *Abnormal response* probably consistent with myocardial ischemia (in the absence of any digitalis therapy) when there was ST segment depression of at least 1 mm (0.1 mv.) on consecutive heartbeats throughout several respiratory cycles.

Procedures for recording and data processing

One hundred one-millivolt standardization signals from the Sanborn 100 Electrocardiograph were recorded in the delay mode for each subject just prior to the exercise test. This provided a mechanism for converting the ECG voltages averaged by the computer to millivolt values. It was essential that the electronic gain controls of the ECG recording system not be altered after the standardization signals were recorded.

A continuous magnetic tape record of the electrocardiogram was made on each subject; this included a resting period (while the subject was seated) of sufficient duration to provide 100 consecutive PQRST cycles, continued through exercise and for at least 3 minutes into recovery after exertion.

The representative summated millivolt calibration and sequential electrocardiograms were prepared from 100 consecutive QRS complexes for each period of rest, exercise and recovery (Fig. 2). Oscilloscopic sweep speed was set to 0.25 second. Each of 400 addresses then had a time duration of 625 microseconds (less 31 for recycling). Stated differently, each 10-millisecond interval (which was the limit of resolution for visual inspection of the clinical ECG recorded at 25 mm. per second) was represented by 16 consecutive voltage addresses. The digital printouts of 400 consecutive summated voltages were examined for maximal and minimal values in order to identify the address locations for the nadirs of Q and S as well as the peak of R. These addresses and voltages were key punched on data cards, along with consecutive voltages for specified addresses (*see below*).

Statistical methods

Voltages were analyzed in order to determine which of these 01-second intervals along the PQ and the ST segments showed the least variation; these intervals were measured from the Q and S nadirs, respectively. The variance was expressed as the coefficient of variation (100 times the standard deviation divided by the mean) of the CAT voltages within the 01 second intervals (16 addresses).

The ST voltage levels relative to their PQ segments were calibrated as follows:

$$ST\ (m\ \ ) = \frac{\text{mean ST} - \text{mean PQ}}{\text{mean millivolt calibration}}$$

where all three variables were expressed in voltage units derived from the digital computer (Fig. 3). This procedure was equivalent to changing the PQ reference segment to zero voltage: voltages from 32 consecutive addresses (0.02-second interval) showing least variance along the PQ segment were averaged for the reference level. The total ST segment was divided into subsegments of 16 consecutive addresses; two such segments showing minimal variance were designated as ST_1 and ST_2. The average voltage of the 16 addresses represented the ST_1 and ST_2 mean voltages. In each instance ST_1 and ST_2 data were obtained for rest, the various workloads of exercise and two periods of recovery.

Significance of differences between means

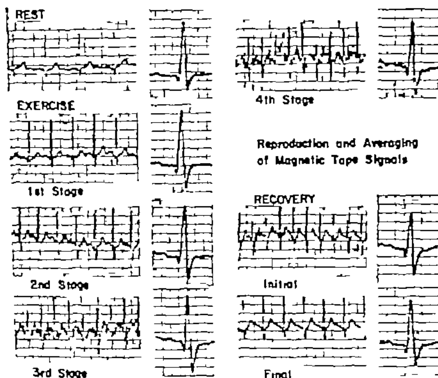


Fig. 2. See text.

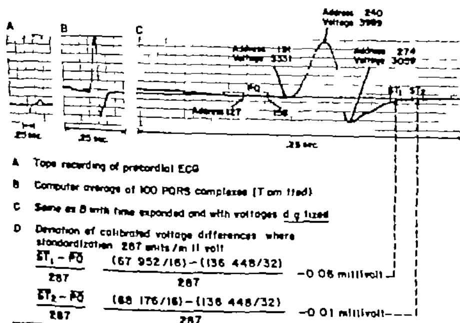


Fig. 3. See text.

was appraised by the students t tests for unpaired data

Results

1 QRS locations and conduction time The Q R and S points were determined from the computer-summated cardiogram for each subject (classified according to clinical postexercise ECG findings) at each stage of exercise From these address locations, QR RS, and QS times were derived

Both R and S points move toward the Q in normal subjects as the workload increases. Table I shows the duration in milliseconds of QR, RS and QS in each subgroup relative to exercise workload as derived from the mean Q R and S locations. The QS interval in normal subjects was shortened The QR fraction appeared to contribute more to this decrease in QS time than did the RS fraction This suggests shortening of the intraventricular conduction time as exercise progresses possibly this is an effect of sympathetic stimulation

The borderline subgroup had the greatest variance in Q R and S address locations. No significant degree of QS shortening was recognized with exercise although again the QR time tended to diminish somewhat with exercise

The abnormal subgroup contrasted with the normal group in the following respects The Q location was qualitatively located earlier in the ECG with exercise whereas with exercise in the normal subjects it was consistently later in relation to the peak of R. The mean QR RS and QS times for the abnormal subjects tend to be greater at any stage of exercise than those for the normal subjects. Possibly this prolongation of conduction time was an expression of myocardial hypoxia

2 Changes in QRS voltages Mean values for Q R and S voltages relative to the mean PQ segment (20 to 40 milliseconds preceding Q) are shown in Table II There was an insignificant decrease in R voltage during exercise in all groups. The normal subjects exhibited a slight (63-microvolt) but significantly ($p < 01$) greater depth of Q with exertion In all subgroups the depth of S was greater by nearly 0 5 millivolt. Whether these changes may be indicative of altered cardiac position or myocardial tension induced by greater diastolic filling of the ventricles in the presence of a high output state or other factors, is unknown.

3 Analysis of variance of PQ and ST segments The variance of individual consecutive 01-second intervals (16 addresses) along the PQ and ST segments was calculated as described in the statistical methods.

Fig 4 displays consecutive coefficients of variation for rest and maximal exercise obtained from the averaged electrocardiograms of 18 clinically normal subjects of whom 6 had normal exercise ECG responses 6 borderline and 6 abnormal The majority of the determinations was below the 1 per cent level of variance, irrespective

Table I Mean durations in milliseconds of QR RS QS intervals in normal subjects classified by postexercise ECG responses

	Normal (30)			Borderline (9)			Abnormal (9)		
	QR	RS	QS	QR	RS	QS	QR	RS	QS
Rest	29 6	20 4	50 0	29 8	19 9	49 7	30 9	20 8	51 7
I	28 7	20 0	48 7	29 7	19 9	49 6	32 8	20 6	53 4
II	27 9	19 9	47 8	29 6	19 7	49 3	32 6	20 8	53 4
III	26 5	19 6	46 1	28 2	19 1	47 3	29 5	21 0	50 5
IV	26 7	20 8	47 5	27 6	20 8	48 4	27 9	23 5	51 4
0 Recovery	25 0	19 5	44 5	8 4	20 2	48 6	28 8	22 4	51 2†
3 Recovery	27 1	21 6	48 7	29 7	20 6	50 3	30 9	22 3	53 2

*$p < .05$ on comparison with resting value for normal subject

†$p < .01$ on comparison with corresponding QS conduction time in normal subject which accelerates from resting values.

Table II *Mean Q R and S voltages for clinically normal men**

Variables	Resting			Maximal exercise			Initial recovery		
	Normal	Border-line	Abnormal	Normal	Border line	Abnormal	Normal	Border line	Abnormal
Q voltage	− 058	− 056	− 090	− 121†	− 043	− 057	− 119†	− 116	− 165
R voltage	1 883	2 407	2 270	1 840	2 075	1 813	1 623	2 018	1 914
S voltage	−0 728	−0 308	−0 814	−1 143†	−1 032†	−1 197	−1 101†	−0 976†	−1 201

*Values in millivolts.
†p < .01.

Table III *Quantitated ST responses for clinically normal men*

	N	ST (mv)	ST (mv)
Rest	73	0 025 ± 0 042	0 040 ± 0 036
I	62	−0 019 ± 0 054	0 007 ± 0 053
II	62	−0 110 ± 0 063	−0 068 ± 0 063
III	61	−0 193 ± 0 122	−0 135 ± 0 098
IV	49	−0 210 ± 0 120	−0 161 ± 0 126
0 Recovery	71	−0 117 ± 0 084	−0 040 ± 0 092
3 Recovery	57	−0 059 ± 0 065	−0 028 ± 0 070

Regardless of clinical interpretation of postexercise ST response

of the clinical electrocardiographic category. The mean coefficient of the PQ segment ranged from 1 to .25 per cent for both rest and maximal exercise. Since the third and fourth .01-second intervals, prior to the Q address, showed the lowest coefficients of variation they were selected as the most reproducible "isoelectric" segments for the voltage reference. PQ voltages referred to hereafter represent the mean of these 32 addresses.

Analysis of the ST segment revealed greater variance in the first three .01 second intervals adjacent to the S nadir. The coefficient was minimal for the subsequent three .01-second intervals. The .01-second intervals beyond that had increments in the variance (due to encroachment of the T wave). Accordingly the fourth and sixth .01-second intervals were selected for appraisal of changes in voltage in the ST interval. These two intervals were designated as ST_1 and ST_2, respectively.

4 Distribution of ST responses The distribution of ST responses for all subjects is tabulated in Table III for rest, each stage of exercise and two recovery periods. There was progressive and significant ($p < .01$) depression of both ST and ST relative to the PQ segment as the workload was increased except from stage III to stage IV (for both ST_1 and ST_2) and from initial recovery to 3-minute recovery for ST_2

Fig. 5 displays the cumulative frequency distributions for the ST voltages classified for each workload. There was a continuum of changes, ranging from negligible to highly significant, which varied with the severity of exertion

Fig. 6 shows the mean ST_1 and ST voltages as a function of exercise stress in the 57 subjects clinically classified by the postexercise visual ECG criteria. ST depression progressed with increasing work loads for each classification of the postexercise ECG responses. The mean S_1

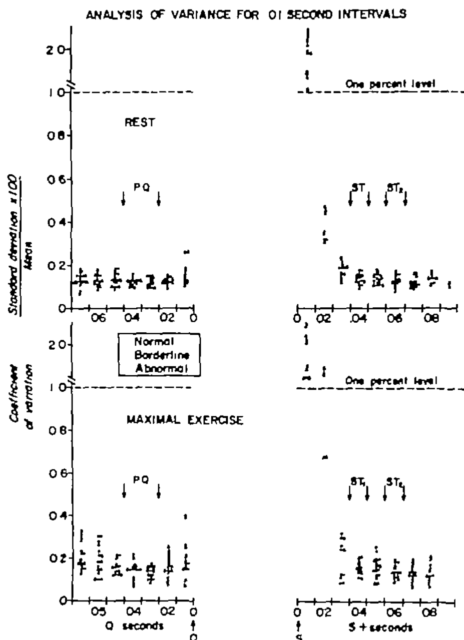


Fig 4 See text

depression for the 9 "abnormal" subjects at maximal exercise was more than 0.3 millivolt The ST depression was proportional *for the three groups* relative to the first three workloads. In the final stage the ST response tended to plateau as did the heart rate Those with more depression of ST also had a more prolonged recovery

5 Reproducibility of the analytic procedure A tape recording of the exercise electrocardiogram for one subject was summated by the computer 20 consecutive times, utilizing 100-beat samples at each workload The standard error of estimate for calibrated ST_1 and ST_2 voltages was expressed in millivolts as follows

	ST	ST
Rest	±0 011	±0 009
Maximal exercise	±0 006	±0 011

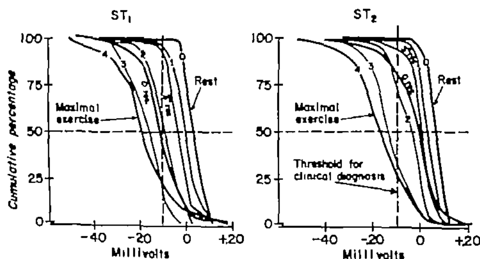


Fig. 5 See text.

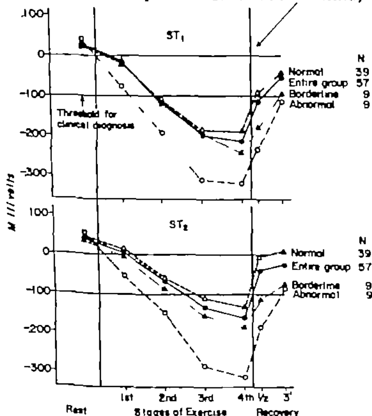


Fig. 6 See text.

Accordingly the standard error of this system was 6 to 11 microvolts, regardless of the workload

Discussion

Clinical interpretation of electrocardiograms with increasing stress of exercise becomes difficult with increasing frequency and amplitude of artifacts. These are caused by surface movements of electrodes with bodily movements and with respiratory variations in the position and volume of the heart relative to the fixed location of the electrodes on the chest wall. Classification of minimal ECG responses may not be possible until exercise is terminated and the *postexercise* ECG is examined It is apparent from this preliminary experience with repetitive summation of the PQRST forces for a fixed number of sequential complexes that these artifactual distortions are largely random events in relation to the cardiac cycle and can be reduced to one tenth of their magnitude when 100-beat samples are averaged The increased sensitivity in detection of significant ECG changes both in amplitude and time duration reveals subtle changes heretofore unrecognized For example ECG changes in exercise are generally related to the early events in ventricular repolarization as reflected in the ST forces, especially the *segment between the nadir* of S or J and the onset of the T wave Such changes have been found in the present data in greater than anticipated magnitude and prevalence in apparently healthy middle-aged men Unsuspected changes in ventricular depolarization in man have been identified also Furthermore detectable alterations in propagation of the excitatory process are different in individuals who show ST changes indicative of ischemia Normal individuals exhibit a deeper initial Q force in the horizontal plane and a significantly shorter intraventricular conduction time Abnormal individuals exhibit an even deeper Q force with no shortening of the conduction time This difference from normal subjects more closely approximates the prolongation of ventricular depolarization noted experimentally by others.[4,7] Similarly the S wave as recorded in this bipolar lead system exhibits a greater depth of similar magnitude in normal borderline and abnormal individuals with respect to the postexercise clinical classification of ST changes.

If the T wave of repolarization of the atria were responsible for the ST depression exhibited in response to strenuous exercise in some individuals, but not in the majority then the greater negative amplitude of the S in the abnormal subjects should also be appreciably greater than it is in the normal group However there is no difference between any of these groups in *the augmented depth of S from the resting* values. As for the changes in the ST segment which were designated in this study as ST_1 and ST_2 it is uncertain whether atrial repolarization extends 60 milliseconds beyond the nadir of S

Possibly the TP segment during diastole would provide a more appropriate reference voltage Samson and Scher[8] demonstrated that myocardial ischemia induced by experimental coronary artery ligation immediately alters the ST segment by more rapid repolarization of injured cells, whereas a decrease in TQ resting potential occurs later Since these forces occur in opposite directions, the difference in voltage between ST and TQ is a summation of both effects. Of greater importance however is the fact that many normal subjects show a *marked shortening or even disappearance* of the TP interval with high heart rates induced by maximal exertion If the subsequent P wave of atrial depolarization falls on the downslope of the preceding T wave of ventricular repolarization the opportunity for identifying the TP segment is lost

In addition to the quantitative objective differences in ST_1 and ST_2 forces, there are qualitative differences by visual inspection which may be referred to as the slope of the ST segment Usually a flat segment or a downslope fusing with an inverted T wave is considered to be a necessary criterion of the ischemic response.[1] Åstrand[9] also emphasized the importance of the shape of the ST segment in evaluation of postexercise changes. With the particular obliquely oriented (V_4 to right scapula) bipolar lead system in the horizontal plane utilized in the present study the ST_1 to ST_2 segment

rarely exhibits a downward slope even in patients with clinical angina pectoris and healed myocardial infarction. Takahashi and associates[18] utilized the EEI lead system proposed by LaDue and associates, and observed that after a double Master two-step test, horizontal or sagging ST depressions are always preceded by junction depressions. In recovery, the ischemic depression usually returned to the isoelectric level without passing through the junction stage. Although this sequence has been observed during the stress of exercise, it has been our clinical experience that some patients do indeed exhibit a return of the junctional depression transiently during recovery. The findings reported here, however, of maximal ST change during maximal exertion are at variance with the final conclusion of Takahashi and associates that the ECG shows more important changes "a few minutes after the cessation of exercise."

It should be emphasized that this automated methodology *rigidly* defines the locations in time after the nadir of S at which voltages of ST segments are quantitated. Secondly, statistical analysis of several representative electrocardiograms from individuals classified as normal, borderline, or abnormal with respect to ST forces clearly demonstrated the optimal loci for ST_1 and ST_2. Thirdly, any error due to data processing is of small magnitude (microvolts), whereas the changes described are of considerably greater magnitude. It is apparent, nevertheless, that further study is indicated, especially in relation to lead systems for spatial vectors and to analysis of successive instants in time. By appropriate refinements in methodology, it may become possible to define the spatial orientation and magnitude of the ST "curve" relative to varying degrees of myocardial ischemia induced by the stress of exercise in the presence of restricted coronary arterial oxygen transport. Suffice it to say that the present studies demonstrate the feasibility of more objective and quantitative analyses of ECG responses to exercise, with less interference from physiologic distortions imposed by high levels of ventilation and artifacts from bodily movements.

The distribution of voltages for ST_1 and ST_2 forces indicate that there is a broad zone of continuous values, as suggested by Takahashi and associates, rather than an obvious qualitative difference, as implied by the usual contemporary clinical definitions. Stated differently, the distribution curve of changes in "normals" is skewed toward greater prevalence of more marked segment depressions. This indicates the contribution of a subset of individuals within the population sampled who have some pathologic basis for coronary insufficiency. Undoubtedly, it will require prolonged longitudinal observations on much larger samples of middle-aged adults to identify which individuals develop clinical manifestations, and to determine a more precise demarcation between an insignificant alteration of ST forces and a significant change consistent with potential or incipient coronary artery disease. The justification for considering these changes to be a manifestation of ischemic heart disease has the sanction of the World Health Organization which recognizes asymptomatic postexercise changes in ST segments and T waves as valid evidence of disease.[11] In the meantime, the arbitrary criteria of −0.15 mv for ST_1 and −0.10 mv for ST_2 when recorded under the conditions of these experiments, appears to be justified for the purposes of preliminary classification of postexercise responses.

Summary

1. A new method is described for dual track, magnetic tape recording of the exercise electrocardiogram and quantitative analysis of successive voltages of 100-beat samples at each workload by means of a computer of average transients. This minimizes respiratory and other distortions and facilitates objective appraisal of responses.

2. Optimal loci, with respect to inherent variability both at rest and during maximal physical exertion of middle-aged healthy men were defined for the PQ reference voltage segment and for parts of the ST segment.

3. The entire group of 57 clinically normal men exhibited progressively more depression of the ST segment with increasing workloads, and considerable resti

tution within 3 minutes of recovery from maximum exertion Even greater ST segment changes were observed in 9 of these men whose postexercise ST responses were visually classified as abnormal prior to automated quantitative analysis

4 Ventricular conduction time was shortened only in normal subjects changes in QRS forces were also detected

5 It is concluded that more quantitative and objective appraisal of ECG responses to exercise is feasible for further studies of the pathophysiology of the ischemic responses as well as epidemiological surveys for detection of individuals with increased risk for subsequent clinical manifestations of coronary heart disease

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The configuration of the P wave during mild exercise

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It has been known that exercise causes the P wave to increase in amplitude, especially in Leads II and III, but the mechanism involved is yet unknown. Some have suggested that it might be attributable to increased potential accompanying enhanced muscular contraction.[1] Since the P wave in normal subjects is less than 200 μV, it has been difficult to detect slight differences in the P wave configuration during exercise with the use of conventional electrocardiographic apparatus. Muscle action potentials can be removed by using special electrodes at specific positions,[2] but because noises from various sources disturb the electrocardiographic pattern, considerable difficulty is encountered in observing the P wave.

Recent advances in electronic computing technique now permit us to obtain the averaged pattern of wave forms complicated by noises. A digital storage oscilloscope (ATAC) was used in this experiment to observe changes in the P wave pattern during exercise.

Methods

A routine electrocardiogram was recorded with surface limb leads from 10 healthy young medical students who ranged in age from 20 to 22 years. It was then recorded on a pulse wave modulation (PWM) type of data recorder having a flat frequency response up to 100 cycles per second (Fig. 1,*A*). Since no appreciable change was noted in the P wave configuration by using a frequency modulation (FM) type of data recorder with a flat frequency response up to 1 kc., a PWM type of recorder was considered to be adequate in recording slow phenomenon such as the P wave. The recorded tape was then *played back in reverse* so that the ECG sequence appeared in the order of T, SRQ, and P. The SRQ wave thus employed for triggering the oscilloscope sweep could display the P wave pattern on the oscilloscope screen (Fig. 1,*B*). By this procedure, which has been reported elsewhere,[3] it was found that the P-Q interval was remarkably constant in normal adults. Thus it was possible to summate the P wave photographically (Fig. 1,*C*). This photographic method, since it is simple and does not require any additional apparatus other than a tape recorder, is convenient, but could not be applied to tracings complicated by noises, such as those accompanying exercise (Fig. 1,*D*).

The average transient computer was

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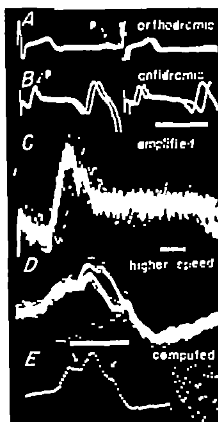


Fig. 1. Method for obtaining averaged P-wave pattern. A, Consecutive cardiac cycles were superimposed photographically on the oscilloscope screen using the QRS spikes as a trigger. Because of respiratory arrhythmia, P and QRS waves are not superimposable. The arrow indicates the location of the P wave. B, When the tape was played back in reverse, successive P waves became superimposable by triggering of the SRQ spikes. Time calibration 0.5 sec. C, The electrocardiogram was then amplified and only the P wave was displayed on the oscilloscope. Time reference 0.05 sec. Note that the P wave is reversed and that the QRS spike is located at the left corner. D, At higher speed of the oscilloscope sweep complete appearance of the P wave can be shown. The tracings are again reversed photographically so that the QRS spike is on the right side. It can also be noted that the P wave temporally changed its pattern in this particular instance. Time 0.05 sec. E, Averaged pattern obtained by digital computer. Arrows indicate the location of the notches. Dots on the right side are overflown signal of the QRS spike. The interval between two dots is 2.5 msec.

found to be most useful in removing such noises unrelated to the true P wave configuration and in improving the signal-to-noise ratio. The summation of 50 to 100 P wave tracings resulted in an averaged P wave pattern as shown in Fig. 1E. The medical data processing computer ATAC 401* was employed to compute this summation. This unit, which is comparable to CAT Mnemotron, has four channel inputs with each channel having 100 addresses. With analysis time set at 250 msec, the interval between two spots in Fig. 1,E is equal to 2.5 msec.

In the exercise test four electrodes which simulated the standard limb leads were attached to the skin with saline paste and fixed in position with adhesive tape, two bilaterally at the infraclavicular region and two bilaterally on the back at the height of the seventh thoracic vertebra. All figures were obtained by summation of 50 consecutive tracings. A standard two-step test was performed.[2,4,5]

Animal experiments were conducted in an attempt to elucidate the mechanism by which the P wave is increased in amplitude during exercise. Five dogs which weighed 6 to 10 kilograms were placed under Nembutal anesthesia and maintained by artificial respiration. The thorax was opened by a sternum-splitting procedure and the heart was cradled in the pericardium to make both the right and left atrium accessible. Warm physiologic saline was applied to the epicardium throughout the experiment. The atrial surface action potentials were recorded with surface bipolar electrodes similar to those employed by Puech and associates.[7] Each electrode consists of a pair of 500 μ silver wires and is insulated up to the tip and shaped like a hook. One electrode was sutured onto the epicardial surface of the right atrium close to the sulcus terminalis, and the other onto the left atrial body. These two pairs of electrodes produced a triphasic action potential, but because of the movement of the electrodes not all of the records showed typical triphasic action potentials.[3]

Results

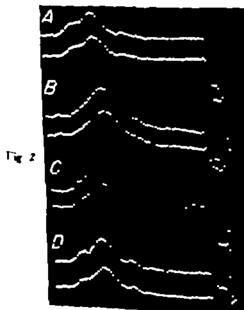
The normal configuration of the averaged P wave. The earlier finding[3] that the P wave of normal subjects has two small notches was confirmed by digital computing technique. The photographic summa-

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tion procedure as shown in Fig 1 *D* is suitable for observing cases in which the P wave constantly changes its pattern during 50 successive cardiac cycles. By digital computing technique such variations in consecutive configurations are all averaged out and information on temporal variations in the P wave pattern as clearly shown in Fig 1,*D* cannot be obtained The P wave in Lead II presents a monophasic tracing and two notches can be distinguished as indicated by arrows in Fig 1,*E* The most evident notch appears at the initial part of the P wave that is, about 0 02 or 0 03 second after the P wave begins. The second notch is not so distinct and could not be differentiated in some P wave patterns but in most instances it could Three or more notches could rarely be observed in the averaged P waves

Effect of exercise. Immediately after exercise was commenced heart rate increased but because the two-step test appears to constitute only mild exercise to the young male students so far studied the effect on the configuration of QRS spikes was not remarkable During exercise the P Q interval decreased slightly and the P wave increased considerably in amplitude Figs. 2 and 3 show the averaged P wave pattern before (*A*) during (*B* and *C*) and after (*D*) exercise In the examples shown in Fig 2 notches on the P wave have disappeared and the P wave assumes a rather smooth pattern Notches can still be noted in Fig 3 but the pattern became somewhat smooth as the amplitude of the P wave increased After exercise the amplitude of the P wave promptly recovered and the notches again became pronounced Among the 10 male subjects so far examined notches disappeared from the P wave in 3 instances, but in 7 instances they persisted There was an invariable increase in amplitude ranging from 16 7 to 63 5 per cent (average—42 8 per cent) Among the 10 subjects, the increase was more than 40 per cent in 7 cases and less than 30 per cent in the other 3 The results obtained in these 3 cases may have been due to the fact that the

Fig 2



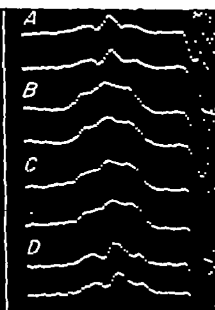


Fig 3

Fig 2 Effect of exercise test on the averaged P-wave pattern. See text for electrode position. *A* Before exercise in standing position *B* and *C*, During mild exercise of two-step test. *D* After test The upper tracing gives Lead III whereas the lower tracing gives Lead II

Fig 3 Effect of exercise on the P wave. *A* Before exercise *B* and *C* During exercise. *D* After exercise An increase in the amplitude of the action potential and smoothing of the P-wave contour are evident

exercise involved in the two-step test was of insufficient magnitude to cause any appreciable change in the P wave pattern for these particular subjects. The P wave vector was strikingly similar in direction in all instances and did not change much during exercise. Only its magnitude was increased in the present mild exercise test.

Animal experiment. In order to ascertain the mechanism involved in the increase in the P wave amplitude during exercise, we performed the following animal experiment. Since the P-Q interval is known to be reduced by the effect of epinephrine, the effect of this drug on the averaged P wave was studied. The top tracing of Fig. 4 is the photographically summated P wave (*P*), the middle tracing is the potential led from the right atrium (*Er*), and the bottom tracing is that from the left atrium (*El*). When epinephrine was administered intravenously, the duration of the P wave shortened remarkably, the amplitude increased, and the notch disappeared, as can be seen in Fig. 4,*2* and 4,*3*. The Er-El interval measured as the distance between the two action potential spikes was also shortened as the amplitude of the P wave increased. In the lower graph of Fig. 4, the P-Q interval (*upper curve*) and the

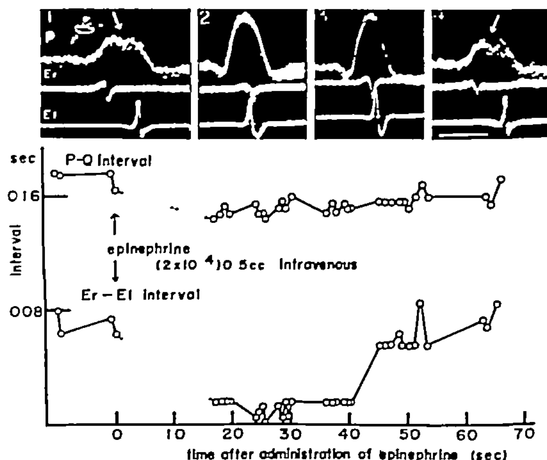


Fig. 4. Changes in the P wave pattern before (*1*), during (*2* and *3*), and after (*4*) the administration of epinephrine. The top tracing indicates the photographically superimposed P wave of dog. Arrows indicate the location of notches. *Er* indicates the potential led from the bipolar electrode sutured onto the right atrium, and *El* that from left atrium. Note the remarkable shortening of the Er-El interval after the administration of epinephrine, which corresponds to the increased amplitude of the P wave. The graph illustrates the temporal changes in the P-Q interval and Er-El interval after the administration of epinephrine. Epinephrine was administered intravenously as indicated by the arrow in the graph.

Er El interval (*lower curve*) were plotted against the time after the administration of epinephrine. After the administration of epinephrine, the interval of the two action potentials remarkably decreased to less than 0.01 second indicating a rather complete synchronization of the two atrial chambers. It may not be correct to assume that tachycardia produced by exercise is identical to tachycardia which develops as an effect of epinephrine. In fact, it has been reported that this analogy does not apply to unanesthetized intact dogs.[8,9] According to the present experiment, tachycardia can be elicited by intravenous administration of epinephrine in anesthetized dogs, and the resulting change in the P wave configuration suggests that the peaked P wave is induced by the synchronization of bilateral atrial excitation.

Discussion

The presence of notches on the P wave has been repeatedly observed by various authors.[3,12-14] Experience has shown that with the use of a highly sensitive oscilloscope small notches can be observed in healthy adults in a fairly high frequency, but many physicians attach no adverse significance to these notches, considering them to be normal variants. It is our opinion that although these small notches may have no pathologic significance, the appearance of them at specific places on the P wave configuration suggests that they might have some physiologic implication. Some workers have observed more than two notches on the amplified P wave[12,13,16] and believe that the P wave consists of potentials of very complicated components. However, from observations of the averaged P wave, two notches appear to be the normal number. Abildskov, Cronvich and Burch[8] graphically predicted the notches on the P wave under the assumption that depolarization spreads in a radial fashion from the sinoatrial node. It seems that the initial notch which we observed on the averaged P wave pattern might correspond to their notch and might be due to the activation of the atrial septum and the left atrium. This possibility was supported by animal experiments, as reported in a previous paper. When multiple surface electrodes were applied on the atrial epicardium, no activity was found to appear from the left atrium during the initial 20 to 30 msec. of the P wave. It is thus reasonable to assume that the initial notch may originate from the addition of left atrial to right atrial depolarization. Reynolds[17] schematically presented P wave patterns of several pathologic conditions by representing two atrial depolarizations with two triangles. Graphical derivation of the P wave configuration by the addition of two triangle components always results in two notches. If the two atria are excited more or less synchronously, the notches should become smaller and the amplitude of the P wave should become larger, as in the case of the exercise test and the epinephrine test. Since Einthoven,[1,18] it has been known that the amplitude of the P wave will increase during physical exertion. The amplitude of an action potential is not directly proportional to the strength of a myocardial contraction, since the action potential represents the membrane phenomenon and is not directly related to the mechanical properties of the myocardium. The increase in the P wave amplitude may not be directly related to the increased force of contraction of atrial muscles during exercise, but it is probably related to the synchronous excitation of bilateral atrial chambers.

Summary

A method of recording the average pattern of the P wave in the normal human electrocardiogram was described. The electrocardiogram was recorded with a tape recorder. The tape was then played back in reverse so that the SRQ spike could trigger the sweep circuit of both the cathode ray oscilloscope and the average transient computer. Fifty consecutive P waves were either superimposed photographically on the oscilloscope screen or computed by the average transient computer. The latter method was found to be suited for the P wave during exercise. The average pattern of the P wave invariably shows two tiny notches. During exertion the amplitude of the P wave increased, the P wave assumed a rather smooth contour, and notches disappeared in some instances. The P wave of the canine heart also increased in amplitude after the intravenous

administration of epinephrine The notches on the P wave disappeared and the peaked P wave was obtained These observations suggest that the mechanism for the increase in the J wave amplitude during exercise might be in part the synchronous excitation of the bilateral atrial chambers

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The simultaneous right and left ventricular outputs in bilharzial cor pulmonale

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The clinical[1] radiologic[2] electrocardiographic[3] and hemodynamic[4,4] features of bilharzial cor pulmonale are well established. The pulmonary hypertension in this disease results from and its degree is related to the organic arterial changes affecting the smaller pulmonary arteries.[6] The pulmonary trunk and its main branches dilate sometimes to aneurysmal sizes[1,7] the dilatation is not always paralleled by the level of the resting pulmonary arterial pressure.[4,6,7] Dyspnea is not a prominent feature of the disease.[1,4] The patients, usually farmers, continue to work for many hours until the disease is advanced. Muscular exercise in bilharzial cor pulmonale raises the pulmonary pressure to high levels, even if it is normal at rest. These high levels during physical effort rather than the resting pulmonary pressure determine the degree of enlargement of the pulmonary artery. Constitutional or acquired weakness of the arterial wall may act as contributing factors. Zaki and his co-workers[7,8] believe that pulmonary arteriovenous bronchopulmonary porto-pulmonary as well as intrasplenic shunts contribute to the hemodynamics of bilharzial cor pulmonale. They claim that these abnormal shunts increase the pulmonary blood flow and explain the disproportionate enlargement of the pulmonary trunk. Shunts from the bronchial artery to the pulmonary artery and from the portal vein to the pulmonary vein should raise the output of the left ventricle over that of the right. We were convinced from our clinical study of a large number of cases of bilharzial cor pulmonale that the left ventricle is not affected clinically radiologically or electrocardiographically. Therefore we studied the simultaneous right and left ventricular outputs in order to decide on this point. We constructed time concentration curves simultaneously from the pulmonary and femoral arteries after injecting a dose of radioiodinated human serum albumin (RIHSA) into the the superior vena cava (SVC). Eventually the appearance time and the mean transit time between the SVC pulmonary artery and femoral artery were determined. The

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circulating blood volume and its distribution in different vascular compartments were also calculated

Material and method

Fifteen patients with uncomplicated bilharzial cor pulmonale and marked dilatation of the pulmonary artery were investigated. In addition 5 males, 16 to 32 years of age who were free of cardiopulmonary diseases were studied as controls. The patients with bilharzial cor pulmonale ranged in age from 11 to 45 years. Thirteen were males and 2 were females. Eight patients (Nos 8 through 15 inclusive) had clinical evidences of valvular incompetence on the right side: 6 of them had pulmonary incompetence and 3 (Nos 9, 11 and 15) had tricuspid incompetence. Patient No 11 had incompetence of both valves. All were compensated except Patient No 9 who was recovering from right heart failure and was receiving digitalis. All were free from respiratory diseases except Patient No 11 who had mild emphysema. All the patients had varying degrees of bilharzial liver fibrosis and splenomegaly and 10 of them had ascites.

All the subjects underwent the routine laboratory investigations, including radiologic and cardiographic examinations. Right sided cardiac catheterization was carried out in the conventional way. A second catheter was introduced into the SVC to be used for the injection of RIHSA. Pressures were recorded by an Elema transducer-electromanometer with the zero level 5 cm below the sternal angle. Oxygen saturations were determined by an Elema oximeter. The pulmonary vascular resistance was calculated on the basis of the right ventricular output as determined by the indicator-dilution technique.

For the determination of the simultaneous right and left ventricular outputs, a volume of RIHSA less than the volume of the cardiac catheter in the SVC was introduced and left in that catheter. The catheter in the pulmonary artery and a Teflon tube in the femoral artery were connected to a twin constant volume sample collector devised by one of us. The constancy *of the volumes of the samples* collected and the applicability of the apparatus *for* quantitative measurements of flow were confirmed.[19] The RIHSA was rapidly delivered into the SVC and sampling from the pulmonary and femoral arteries was begun and continued at 1 second intervals for 35 seconds. The radioactivity of the injected amount and of each of the samples was read in a well scintillation counter. Ten minutes after the injection of RIHSA a sample of heparinized blood was drawn from the pulmonary artery for calculation of the total blood volume.

Time concentration curves were recorded from both the pulmonary and femoral arteries. A semilogarithmic plot of the time concentration curves was also made: the downslope was extrapolated to a level corresponding to 1 per cent of the peak concentration.

The mean transit time (T_m) was calculated according to the equation

$$T_m = \frac{\Sigma ct}{\Sigma c}$$

where c and t are the respective concentration and time in seconds from the start of injection (the effects of recirculation being eliminated). The blood volume in different compartments (V) was calculated according to the equation

$$V = \frac{F \times T_m}{60}$$

where F = cardiac output and T_m = mean transit time across the compartment. The average of the simultaneous right and left ventricular outputs was taken as F.

Results

Hemodynamic data. The important hemodynamic data are summarized in Table I. The arterial oxygen saturation ranged between 94 and 98 per cent in all 15 patients, except Patient No 11 who had mild emphysema and an obstructive ventilatory defect: his arterial oxygen saturation was 92 per cent. His pulmonary arterial pressure was not affected by the inhalation of oxygen which raised his arterial oxygen saturation to 96.5 per cent, indicating that hypoxia did not contribute to his vascular pulmonary hypertension.

Simultaneous right and left ventricular outputs (Table II). In the control group

Table I Hemodynamic data

Patient number	Age Sex	BSA (M^2)	Pulmonary artery: Size	Pulmonary artery: Pressure (mm Hg) Systolic	Diastolic	Mean	PCP (mm Hg)	FA (% O saturation)	PVR (units)	Cardiac output (L./min.) RV	LV
Bilharzial cor pulmonale											
1	32, M	1 81	II	38	15	23	8	94 5	2 3	6 43	6 42
2.	38 M	1 65	II	36	19	25	3	96 0	3 1	6 46	6 41
3.	20 M	1 29	III	39	19	26	4	97 0	4 5	4 93	4 64
4	29 M	1 67	IIIA	46	25	32	4	98 0	5 1	5 46	5 34
5	20 M	1 52	IIIA	50	25	33	3	95 5	6 6	4 55	4 63
6.	11 M	1 04	II	52	24	33	4	96 0	3 8	4 22	4 08
7	45 M	1 62	III	65	29	41	9	96 5	5 8	5 75	5 68
8.	29 M	1 52	IIIA	65	27	41	0	94 0	8 5	4 70	4 85
9	13 F	0 97	III	65	33	44	9	97 0	17 6	1 93	1 99
10	13 M	1 15	III	68	34	45	7	94 0	14 5	2 62	2 69
11	43 M	1 82	III	70	43	52	7	92 0	18 0	3 11	3 10
12.	15 M	1 35	III	78	42	54	2	97 0	14 5	3 86	3 74
13	36, M	1 65	IIIA	86	43	57	5	97 5	11 0	4 07	3 87
14	35 M	1 53	III	99	37	58	10	94 5	10 8	4 44	4 25
15	25, F	1 72	III	72	58	63	3	94 0	13 6	4 41	4 13
Control											
16.	27 M	1 75	0	16	7	10	6	96	1 2	3 31	3 28
17	16, M	1 30	0	11	6	8	2	96	1 7	3 47	3 58
18.	27 M	1 76	0	14	5	8	5	98	0 5	5 88	5 85
19	16, M	1 50	0	18	7	11	2	97 5	1 4	6 24	6 23
								98		5 38	5 50
20.	32 M	1 64	0	14	6	9	0	98	1 6	5 65	5 87

BSA Body surface area, in square meters. PCP: Pulmonary capillary pressure. FA Femoral artery. PVR Pulmonary vascular resistance. RV Right ventricle. LV Left ventricle. Pulmonary artery size—0 = Normal cardiac waist. II = Slight bulging of cardiac waist. III = Marked bulging of cardiac waist. IIIA = Aneurysmal dilatation.

two estimations of the right and left outputs were made in Patient No 19 within half an hour we thus had six determinations in these 5 subjects. In three of these determinations the left ventricular index was 3.4 2.2 and 3.9 per cent higher than the right. In the other three determinations the left ventricular index was 2 2 0.3 and 0.2 per cent less than the right. In Patient No 19 the left index was 0.2 per cent less than the right on the first occasion and 2.2 per cent higher than the right on the second determination. In all six determinations the left ventricular index averaged 1 13 per cent more than the right (S D = 2.4 per cent S E. = 0 98 per cent, t = 1 16 per cent at the 95 per cent level i.e nonsignificant)

Of the 15 patients with bilharzial cor pulmonale 9 showed a left ventricular index 0 6 to 6 7 per cent less than the right ventricular index, with a mean of 3 9 per cent. In 4 patients the left ventricular index was 2.0 to 2 9 per cent higher than the right, with a mean of 2 6 per cent. In the other 2 patients the right and left ventricular indices were equal. In all 15 patients the left ventricular index averaged 1 48 per cent less than the right (S D = 3 35 per cent S.E. = 0.86 per cent, t = 1 6 at the 95 per cent level i e nonsignificant)

Circulation times (Table III)

THE APPEARANCE TIMES The appearance times between the SVC and the pulmonary and femoral arteries showed no significant changes between the groups studied

MEAN SVC PULMONARY ARTERY CIRCULATION TIME. In the control group it ranged between 5 3 and 6 9 seconds, with an average of 5 9 seconds. In the group with

Table II Simultaneous right and left cardiac outputs

Patient number	RV index	LV index	Δ L − R (%)
Bilharzial cor pulmonale			
1	3 47	3 47	0
2	3 88	3 88	0
3	3 83	3 59	−6 7
4	3 27	3 20	−2 2
5	2 99	3 05	+2 0
6	4 06	3 92	−3 6
7	3 16	3 12	−1 3
8	3 10	3 19	+2 8
9	1 99	2 05	+2 9
10	2 28	2 34	+2 6
11	1 72	1 71	−0 6
12	2 86	2 77	−3 2
13	2 43	2 34	−3 8
14	2 90	2 78	−4 3
15	2 56	2 40	−6 7
			Mean = −1 48
Control			
16	2 31	2 29	−2 2
17	2 31	2 39	+3 4
18	3 34	3 33	−0 3
19	4 16	4 15	−0 2
	3 59	3 67	+2 2
20.	3 44	3 58	+3 9
			Mean = +1 13†

*Standard deviation 3 35 per cent Standard error 0 86 per cent t 1
†Standard deviation 2 4 per cent Standard error = 0 99 per cent 1 16.
RV Right ventricular LV Left ventricular

Table III Circulation times

	Number of cases	SVC − PA (time in seconds)		SVC − FA (time in seconds)		PA − FA (time in seconds)	
		AP	T_m	AP	T_m	AP	T_m
Control	6	1 7 (1 2)*	5 9 (5 3 6 9)	9 0 (6 12)	15 5 (13 0 18 5)	7 3 (5 10)	9 6 (7 7 12 8)
Bilharzial cor pulmonale							
Without valvular incompetence	7	1 6 (1 2)	6 6 (4 8 8 6)	8 3 (5 10)	15 6 (10 3 19 3)	6 7 (4 9)	9 0 (5 1 11 7)
With valvular incompetence	8	2 0 (1 3)	10 6 (7 4 14 3)	10 0 (6 13)	23 0 (15 8 27 0)	8 0 (5 11)	12 4 (8 4 16 1)

*Range is given in parentheses.
SVC Superior vena cava. PA Pulmonary artery FA Femoral artery AP Appearance time T_m Mean transit time

cor pulmonale it ranged between 4 8 and 14 3 seconds, with a mean of 8 8 seconds In the patients without valvular incompetence it averaged 6.6 seconds whereas in those with pulmonary or tricuspid incompetence it averaged 10 6 seconds.

MEAN SVC–FEMORAL ARTERY CIRCULATION TIME. In the control group it ranged between 13 and 18.5 seconds, with an average of 15.5 seconds. In the group with cor pulmonale it ranged between 10 3 and 27 seconds with an average of 19 6 seconds. In the patients without valvular incompetence it averaged 15 6 seconds, whereas in those with pulmonary and/or tricuspid incompetence it averaged 23 seconds.

MEAN PULMONARY ARTERY–FEMORAL ARTERY CIRCULATION TIME. In the control group it ranged between 7 7 and 12 8 seconds, with an average of 9 6 seconds. In the group with cor pulmonale it ranged between 5 1 and 16 1 seconds with an average of 10 8 seconds. In the patients without valvular incompetence it averaged 9 seconds whereas in those with valvular incompetence it averaged 12 4 seconds.

Blood Volumes (Table IV)

TOTAL BLOOD VOLUME PER METER OF BODY SURFACE AREA. In the control group it ranged between 3 070 and 3,540 ml /M² with a mean of 3,250 In the group with bilharzial cor pulmonale it ranged between 2,230 and 4 090 ml /M² with a mean of 3,270

RIGHT CARDIAC VOLUME. In the control group it ranged between 227 and 416 ml /M² with a mean of 314 In the patients with bilharzial cor pulmonale it ranged between 278 and 697 ml /M² with a mean of 410 ml./M² In those without valvular incompetence it averaged 387 ml /M² whereas in those with pulmonary and/or tricuspid incompetence it averaged 430 ml /M²

CENTRAL BLOOD VOLUME. In the control group it ranged between 581 and 1 045 ml./M² with a mean of 821 ml /M² In the group with bilharzial cor pulmonale it ranged between 687 and 1 403 ml /M² with a mean of 918 ml /M² In the patients without valvular incompetence it averaged 899 ml /M² whereas in those with pulmonary and or tricuspid incompetence it averaged 935 ml./M²

BLOOD VOLUME BETWEEN PULMONARY AND FEMORAL ARTERIES The blood volume in this compartment in the control group ranged between 314 and 630 ml /M² with a mean of 507 ml /M² In the patients with bilharzial cor pulmonale it ranged between 341 and 756 ml /M² with a mean of 509 ml /M² In the patients without valvular incompetence it averaged 513 ml /M² whereas in those with pulmonary and or tricuspid incompetence it averaged 505 ml /M²

Discussion

The 15 patients with bilharzial cor pulmonale who were studied had moderate to severe pulmonary hypertension their mean pulmonary arterial pressure ranged between 23 and 63 mm Hg and their

Table IV Blood volumes

	Number of cases	Total blood vol me (ml /M²)	Right cardiac volume (ml./M²)	Central blood vol me (ml /M²)	CBV – RCV (ml /M²)
Control	6	3 250 (3 070–3 540)*	314 (227–416)	821 (581 1 045)	507 (314–630)
Bilharzial cor pulmonale					
Without valvular incompetence	7	3 100 (2 230–3 920)	387 (278–440)	899 (687 1 196)	513 (341–756)
With valvular incompetence	8	3 410 (2 800–4 090)	430 (327–697)	935 (735–1 403)	505 (394 706)

*Range is given in parentheses.
CBV-RCV Central blood volume–Right cardiac volume.

pulmonary vascular resistance ranged between 2.3 and 18 units (Table I). The 8 patients who had valvular incompetence on the right side had a mean pulmonary arterial pressure above 40 mm. Hg and a pulmonary vascular resistance above 8 units. As the disease progressed, the valves of the right heart yielded before the increasing pressure load. We intentionally chose patients with evident dilatation of the pulmonary artery. 3 of the 15 patients had slight bulging of the cardiac waist (Grade II enlargement of the pulmonary artery). The other 12 patients had marked bulging of the cardiac waist with enlargement of the main pulmonary branches (Grade III) which amounted to aneurysmal dilatation in 4 of them. The discrepancy between the size of the pulmonary artery and the resting pulmonary arterial pressure was evident (Table I). These patients were thus especially suitable for the study of the existence of the pulmonary shunts claimed by Zaki and associates[7,8] to be hemodynamically significant.

The appearance times between the SVC, pulmonary artery, and femoral artery in the patients with bilharzial cor pulmonale did not differ from the appearance times in the control group. This was expected because these patients did not have heart failure. In the 7 patients without valvular incompetence on the right side the mean transit times between the SVC, pulmonary artery, and femoral artery were normal, but in the 8 patients with more advanced disease and valvular incompetence on the right side, the mean transit times were prolonged. Valvular regurgitation produced spreading of the dilution curves, and the mean transit time between the SVC and pulmonary artery was prolonged. The delay in the mean transit time between the pulmonary artery and the femoral artery in these 8 patients was probably due to the very high pulmonary vascular resistances. In the 7 patients without incompetence the pulmonary vascular resistance was not sufficiently high to produce impedance to flow in the pulmonary circuit.

As can be seen from Table IV and Fig. 1, the central blood volume (between the SVC and femoral artery) was increased in the patients with bilharzial cor pulmonale. The increase was limited to the compartment between the SVC and the pulmonary trunk, leaving the pulmonary blood volume normal. The pulmonary hypertension produced some dilatation of the right heart and marked dilatation of the main pulmonary artery. The cardiac dilatation was more evident in the patients with valvular incompetence.

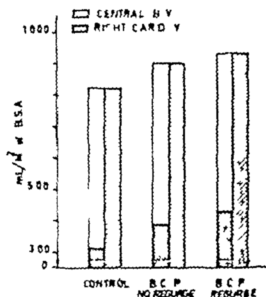


Fig. 1. Blood volumes. B.C.P., Bilharzial cor pulmonale. Regurge, Pulmonary and/or tricuspid regurgitation. C.B.V., Central blood volume (between the superior vena cava and femoral artery). Right Card. V., Right cardiac volume (between the superior vena cava and pulmonary artery).

In the 5 normal control subjects, six determinations of the simultaneous right and left ventricular outputs were obtained. The difference between the left and right outputs was statistically nonsignificant at the 95 per cent level. Cudkowicz and associates, using a similar technique in 5 normal subjects, found that the left ventricular output averaged 0.4 per cent more than the right. They suggested that the difference might represent the part of the bronchial circulation that drains normally in the pulmonary veins. Review of the figures obtained by Cudkowicz and associates showed that the differences that they had were similar to our findings and were statistically nonsignificant. Nonsignificant differences were also reported by Nakamura[11] in normal subjects.

In our normal control Patient No. 19

simultaneous right and left ventricular outputs were determined twice within half an hour. In the first determination the left output was 0.2 per cent less than the right and in the second determination it was 1.2 per cent higher. When we applied our technique on a model circulation[1] in which there was no possibility of a bronchial blood flow we had the same type of insignificant differences. Thus it can be safely concluded that the technique of simultaneous determination of right and left ventricular outputs which was employed by Cudkowicz, Nakamura, and ourselves cannot detect the part of the bronchial circulation which drains in the pulmonary veins in the *normal subject*. On the other hand, in diseases in which bronchopulmonary shunts have been proved to exist this method was able to detect and quantitate these shunts.[12, 13]

In the patients with bilharzial cor pulmonale the difference between the simultaneous left and right ventricular outputs was statistically nonsignificant. If bronchopulmonary shunts of a degree such as those reported by Foda[14] (12 to 47 per cent of the left ventricular output) were present, the left ventricular output should be *significantly* higher than the right. Appreciable portopulmonary shunts, if present, should produce the same effect; they should also lead to arterial oxygen desaturation. In the present series, the arterial oxygen saturation was *normal* except in Patient No. 11 who had obstructive ventilatory insufficiency which did not contribute to his pulmonary hypertension and his arterial oxygen saturation was corrected by the inhalation of oxygen. Our previous studies,[1, 3] as well as those of Ibrahim and associates,[4] showed that arterial oxygen desaturation is not a feature in uncomplicated bilharzial cor pulmonale.

The shape of the dilution curves in bilharzial cor pulmonale was regular and smooth (Fig. 2). The right and left curves had the same shape and were similar to the curves obtained in the control group. Valvular incompetence on the right side expanded the right curves, and subsequently the left curves. This occurred in all of our patients who had tricuspid or pulmonary valvular incompetence but

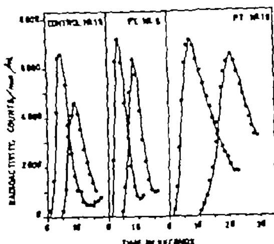


Fig. 2. Dye dilution curves recorded simultaneously from the pulmonary artery (*open dots*) and the femoral artery (*solid dots*). *Control* No. 16, Normal. *Pt. No. 6*, Bilharzial cor pulmonale without valvular incompetence. *Pt. No. 10*, Bilharzial cor pulmonale with pulmonary incompetence.

the right and left curves were still healthy and smooth (Fig. 2). Significant bronchopulmonary or portopulmonary shunts should produce differences between the shapes of the right and left curves. Whereas the former would remain normal, the latter would show slurring prolongation of the downslope with multiple humps due to recirculation of the indicator through the short circuits.

Our results demonstrated clearly that in bilharzial cor pulmonale there is no significant difference between the right and left ventricular outputs, and the dilution curves did not show evidence of shunts. Moreover, our findings that the pulmonary blood volume was not increased can also be taken as another evidence for the absence of significant shunts to the pulmonary circuit. Shunts to the pulmonary circuit should increase the load on the left ventricle, but the left ventricle in uncomplicated bilharzial cor pulmonale is clinically, electrocardiographically, and radiologically normal even in the most advanced cases. There is no hemodynamic or pathologic evidence of increase in its work.

Thus we can conclude that bronchopulmonary and portopulmonary shunts, if present, do not contribute to the hemodynamics of bilharzial cor pulmonale

The degree of pulmonary hypertension in this disease is parallel to the degree of organic vascular changes affecting the small pulmonary arteries. Pulmonary arteriography[2,4] demonstrated that the degree of arterial changes was related to the height of the pulmonary pressure and vascular resistance. Postmortem pulmonary arteriography[2] revealed that there was a curvilinear relationship between the degree of arterial changes and the hypertrophy of the right ventricle. The grade of right ventricular hypertrophy as revealed by the electrocardiogram was also related to the pulmonary vascular resistance.

Summary

The claim that bronchopulmonary and/or portopulmonary shunts explain the disproportionate increase in the size of the pulmonary artery and contribute to the hemodynamics of bilharzial cor pulmonale was the subject of this study. We determined the simultaneous right and left ventricular outputs in 20 subjects: 5 normal controls and 15 patients with bilharzial cor pulmonale who had marked enlargement of the pulmonary artery. In addition to pressures, the pulmonary vascular resistance, circulation times, and blood volumes in the different compartments were measured. Our results showed that in bilharzial cor pulmonale there was no difference between the outputs of the right and the left ventricles to suggest that any significant shunt was operating. This agrees with the normality of the left ventricle, clinically, radiologically, and electrocardiographically, in uncomplicated bilharzial cor pulmonale. As the disease advances, valvular incompetence on the right side develops. The very high pulmonary vascular resistance prolongs the mean transit time across the pulmonary circuit. The pulmonary blood volume remains normal but the right cardiac volume increases.

The exposure to higher pulmonary pressures during hours of activity as well as the possibility of weak and yielding pulmonary arterial walls are still valid explanations for the discrepancy between the size of the pulmonary artery and the pressure in it during rest.

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Temporal dispersion of recovery of excitability in atrium and ventricle as a function of heart rate

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Patients with complete heart block must depend upon idioventricular pacemaker activity recurring at a frequency high enough to maintain an adequate cardiac output. Judging from the results of studies in isolated ventricular tissue,[1] the desirable idioventricular focus probably resides in the specialized conducting tissue in which the slow diastolic depolarization characteristic of "true" pacemakers is commonly observed. "Ectopic" activity, that is, premature nonpacemaker impulse generation, is not so desirable, for it represents a mechanism which, at least potentially, may lead to ventricular flutter or fibrillation.

In patients with complete A-V dissociation it has been observed that early ectopic beats occur more frequently when the basic idioventricular rate is slow, and it is believed that the danger of transient or fatal episodes of ventricular fibrillation is also increased at slow frequencies.[2,3] (One would expect, of course, that episodes of ventricular arrest would also be more likely when the intraventricular pacemaker is slow.) When the ventricular frequency was increased by electrical stimulation or by infusion of catecholamines, the incidence of early ectopic beats decreased.[2,3]

Related observations have been reported by Langendorf and associates.[4] In a group of cases (predominantly atrial fibrillation) in which ventricular premature beats occurred at a fixed coupling interval, the ectopic beats occurred only when the R-R interval preceding the couplet was relatively long.

Asynchrony of recovery of excitability in the myocardium must be an important factor in the genesis of ectopic activity and fibrillation of the heart.[5-7] Closely coupled premature beats, as in bigeminal rhythm, may be the result of the difference in potential between cells which repolarize early and closely adjacent neighbors which recover later. It follows that the greater the range of action potential durations among closely adjacent fibers, the greater the chance of the ectopic mechanism. The observed effect of ventricular frequency in the clinical observations suggests that the

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range of refractory periods (RP) and action potential durations may be greater at low basic frequencies than at higher rates. In other words it seems to be likely that the frequency distribution of refractory periods should cover a greater range when the mean RP duration is longer as it would be at slow heart rates.

The present experiments were undertaken to estimate the range of variation of refractory periods in the atrium and in the ventricle and the vulnerability of these tissues to the development of ectopic activity and fibrillation at different basic driving frequencies. Action potential durations in isolated ventricular tissue were also measured at various driving frequencies. The results of these experiments suggest that the generation of ectopic impulses at slow basic rates may be due to temporal dispersion of the recovery process.

Methods

For experiments on hearts in situ, mongrel dogs weighing from 9 to 18 kilograms were anesthetized by intravenous injection of sodium pentobarbital, 35 mg. per kilogram. Under artificial respiration the chest was opened in the midline and the pericardium was opened to expose the anterior surface of the heart. In all experiments the vagi were cut, and the stellate and upper thoracic sympathetic ganglia were excised on both sides. The S-A node was usually inactivated by crushing to permit observations at low heart rates.

The unipolar stimulating electrode used to determine the refractory period was made of tungsten wire with a diameter of 0.12 mm. and designed to allow its tip to penetrate only about 0.6 mm. deep into the epicardium and to ride freely with movement of the heart. A variable interval generator was used to trigger a Tektronix pulse generator which delivered rectangular pulses of variable interval, duration and intensity through an isolation transformer to the unipolar cathode and an indifferent anode in the chest wall. At each placement of the electrode at a chosen point and at each driving frequency the threshold stimulating voltage was determined using stimuli of 2 msec. duration and the heart was driven by basic stimuli (S_1) of 1.5 times the threshold voltage. The refractory period was then estimated using a test stimulus (S_2) of the same duration and intensity fired at variable intervals after every twelfth basic S_1. Responses recorded from a pair of bipolar electrodes placed at a distance of about 8 mm. from the site of stimulation were used to indicate the success or failure of S_2 in evoking a propagated response. The interval between S_1 and the earliest successful S_2 was recorded as an estimate of the refractory period. The S_1S_2 intervals were read from a calibrated oscilloscope screen and were sometimes recorded together with the response on a Grass polygraph.

For determination of the ventricular fibrillation threshold, a pair of bipolar electrodes was attached to the ventricle. These electrodes were small steel hooks separated by a distance of about 1 mm. Two Tektronix pulse generators (A and B) were driven by the variable-interval generator. Pulse generator A was used to deliver the basic driving stimuli (S_1) through an isolation transformer and B was triggered to fire a single pulse at any controlled interval following the twelfth basic S_1. This pulse was then used to trigger a Grass stimulator which provided a synchronized test stimulus (S_2) of 10-msec. duration and up to 35 Ma. through a stimulus isolation unit. The output of the Grass stimulator was connected in series with that of pulse generator A to provide independently variable S_1 and S_2 stimuli to the ventricle through the same bipolar electrodes. The S_1S_2 interval was varied to scan the vulnerable period and the intensity of the stimulus was increased progressively until fibrillation occurred. The strength of the stimulus was recorded on an oscilloscope by means of a Tektronix current probe amplifier.

For studies with isolated tissue, pieces of right ventricular wall were excised from the hearts of dogs anesthetized with 30 mg. per kilogram of sodium pentobarbital. The tissue was perfused with Tyrode's solution equilibrated with a mixture of 95 per cent oxygen and 5 per cent carbon dioxide. Temperature of the bath was maintained at 36-37°C. The preparation was driven at various basic cycle

lengths by bipolar stimuli of 5-msec. duration and two times the threshold stimulating voltage. Intracellular action potentials were recorded from subendocardial fibers with glass capillary microelectrodes filled with 3M KCl. Electrode resistances ranged from 10 to 30 megohms. The recording instruments included a Grass cathode follower and D C amplifier a Tektronix oscilloscope and a Grass camera.

Results

Asynchrony of recovery of excitability Refractory periods were measured at six randomly selected points on the right atrial surface at a number of basic driving frequencies in six experiments. The results of one of these are illustrated in Fig 1 Individual values of the RP estimated with test stimuli of 1.5 times the diastolic threshold at each of seven basic cycle lengths, are plotted in the upper portion of the figure. The mean values and the standard deviation are plotted in the middle graph and the range of variation as the stippled bars at the bottom of the figure. At the highest driving frequency

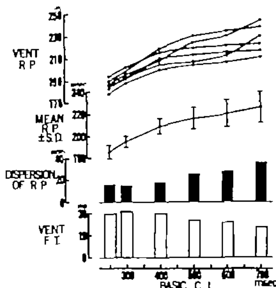


Fig 2 Exp 12-9-64. Variability of refractory periods and the fibrillation threshold in the ventricle t nous basic cycle lengths.

the range of dispersion was 24 msec or about ± 8 per cent of the mean value. At the lowest frequency (basic cycle 600 msec.) the range was increased to 56 msec or about ± 12 per cent of the mean

Temporal dispersion of recovery was similarly estimated in the right ventricle, with similar results. Refractory period durations were more tightly grouped but the spread of recorded values increased as the driving frequency was diminished In the experiment of Fig 2 the minimum range was 16 msec at a cycle length of 300 msec increasing to 34 msec at a cycle length of 700 msec

Similar findings were consistently observed in all experiments. Average values of temporal dispersion of atrial and ventricular refractory periods in six experiments are plotted as bar graphs in Fig 3 In both tissues the maximum ranges, 55 msec in the atrium and 43 msec in the ventricle were recorded at the slowest driving frequencies. Minimal values of 28 and 21 msec respectively were obtained at a basic cycle length of 250 msec in the atrium and 300 in the ventricle. The slightly higher spread at the shortest cycle length studied in each tissue was regularly observed suggesting that dis-

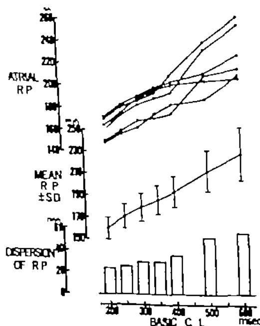


Fig 1 Exp. 9-21-64 Range of ariation of refractory periods in the atrium t various basic y le lengths

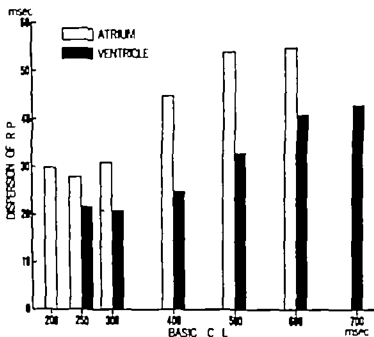


Fig 3 The range of dispersion of refractory period in the atria and in the ventricles at various basic cycle lengths. Average values in 6 experiments. Analysis of variance indicates that the RP dispersion in both tissues is a significant function of the cycle length at the level of $p < 0.01$

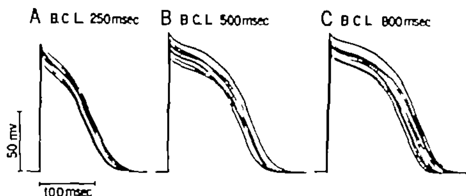


Fig 4 Exp. 10-27-64 Temporal dispersion of transmembrane action potential duration in 8 ventricular fibers at three basic cycle lengths.

persion of recovery might be further increased at very high frequencies.

The results obtained in the isolated tissue preparations were comparable. In three experiments, transmembrane action potentials were recorded from several subendocardial sites in the free wall of the right ventricle at each of three basic cycle lengths. In Fig 4 action potentials obtained at eight different puncture sites were retraced and superimposed at basic cycles of 250 500 and 800 msec Measured to the time of 50 per cent repolarization the range of action potential durations was 19 msec at the cycle length of 250 msec 25 msec at 500 and 35 msec at 800

Vulnerability to fibrillation No attempt was made to assess the vulnerable period of the atrium in these experiments, but in the estimations of atrial RP the earliest successful S_2 stimulus at slower basic frequencies was frequently followed by a

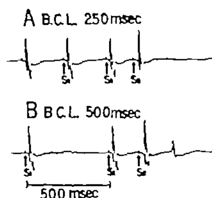


Fig. 5. Exp. 11-24-64. Earliest effective premature stimulus (S_2) at 1.5 times threshold evokes spontaneous coupled discharge at low basic frequency (*B*) but not at higher frequency (*A*).

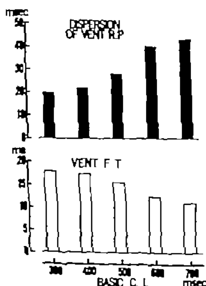


Fig. 6. Analysis of variance indicates significant effect of cycle length on RP dispersion ($p < 0.01$) and on fibrillation threshold ($p < 0.05$).

double response. The records in Fig. 5 were obtained at basic driving frequencies of 4 per second in *A* and 2 per second in *B*. The earliest successful S_2 evoked a single response in *A*, but the evoked response was followed by a spontaneous discharge at the slower frequency.

Ventricular fibrillation thresholds were measured at several basic driving frequencies. An inverse relationship was demonstrated between basic cycle length and fibrillation threshold in all experiments. In the experiment illustrated in Fig. 2, for example, the threshold decreased from 20 Ma. at the fastest frequency to 14 Ma. at the slowest frequency. The average values in four experiments are plotted in Fig. 6. The ventricles were regularly more vulnerable to fibrillation when asynchrony of recovery of excitability was increased at low driving frequencies.

Discussion

Dispersion of refractory period durations. At regular driving frequencies, the degree of temporal dispersion of recovery from the refractory state in atrium and ventricle appears to be directly related to some function of the refractory period, which in turn is a function of the basic cycle length. It is not surprising that the relationship between these variables is not precisely the same at all sites within the atria or ventricles, for the immediate environment of individual fibers with respect to such variables as ionic concentrations, gas tensions, temperature, mechanical tension, and neurohumoral mediators can be neither uniform nor constant. Some inherent inhomogeneity must be expected. The basic equations relating cycle length and RP of individual elements must, however, be similar; only the constants would be expected to differ from one site to another. Given the empirical equation $R = K\sqrt{C}$, for example, where R and C represent refractory period and cycle length, respectively, the range of refractory periods at any given frequency would depend on the range of the individual values of *K*, and the temporal dispersion of *R* would, of course, increase as *C* increases. This was found to be true (Figs. 1 and 2).

The true dispersion of recovery times could be established only by estimating the refractory periods of a large number of individual cells. The technique used in the intact heart experiments must always, within the effective range of the stimulus, select those fibers having the briefest RP. Unless the fibers within rather gross areas of tissue have identical properties, the true range must, therefore, be greater than the recorded values. The range of action potential durations recorded in the limited number of observations re-

ported here did not exceed the RP dispersion in the intact heart at comparable driving frequencies, but the refractory periods of the individual cells were not measured.

In all experiments and at all frequencies studied the dispersion observed in the atrium exceeded that in the ventricle. Whatever the reason for the difference, it probably accounts for the fact that multiple responses to test stimuli of 1.5 times threshold were commonly observed at slow driving frequencies in the atrium but never in the ventricle; stronger stimuli approaching the fibrillation threshold will of course initiate multiple responses in the ventricle as well.

Dispersion of recovery tended to increase slightly but regularly at the highest driving frequencies studied. When the maximum frequency the tissue can follow is approached, complete recovery of excitability may not occur between responses. If the driving stimuli recur before expiration of the relatively refractory period of some elements, but after full recovery of others, increased dispersion may occur. It has already been demonstrated that the range of refractory periods for early premature responses is increased and that the fibrillation threshold is correspondingly reduced as compared with responses initiated after complete recovery.

Relationship to ectopic impulse generation. Asynchrony of recovery from the refractory state provides a field in which a premature stimulus may induce fractionation and repetitive activity. It has never been established that the initial repetitive responses result from re-entry in the sense that a round trip passage is successfully completed by slow propagation through a circuit of limited dimensions. Although such circuits are not only possible, but probably inevitable when dephasing of major degree results after a number of closely coupled repetitive discharges, they do not satisfactorily explain the genesis of the first premature response in the absence of external stimulation. For example, dispersion is greatest at the lowest driving frequencies, but the mean RP duration is also prolonged. The latter effect should prevent re-entry. Yet the generation of spontaneous ectopic impulses in the clinical situation is more common at slow frequencies.[1,2]

The likeliest mechanism of generation of spontaneous impulses is re-excitation of already repolarized elements by the flow of current between these and neighboring elements which are still depolarized. When neighboring fibers recover within a few milliseconds of each other, re-excitation cannot occur, for the difference in potential between them will not exceed threshold; but increased temporal dispersion would set up the appropriate conditions. Accordingly, spontaneous, closely coupled ectopic beats would be more likely at slow basic frequencies. The site at which these events occur may well be at junctions between myocardial cells and the specialized conducting system, for the action potentials of ventricular muscle and peripheral Purkinje fibers are widely disparate, particularly at low driving frequencies.[17]

Spontaneous beats of this nature were not observed in the present experiments, except when dispersion was presumably compounded by an early premature stimulus in the atrium (Fig. 5). However, the fibrillation threshold in the ventricle was significantly diminished at slow heart rates. This suggests that the frequency-dependent dephasing does indeed set the stage for self-sustained spontaneous activity. A related observation was made by Alessi and associates[1] who found that fibrillation commonly followed a single premature stimulus applied at a point on the atrial surface at which vagally induced abbreviation of the RP was pronounced.

The observation that ectopic activity is common at slow heart rates in patients with complete heart block can be readily explained in terms of the present results. Closely coupled ectopic beats, not of true pacemaker origin, should be more common at slow rates, particularly in the presence of additional factors contributing to inhomogeneity, such as irregular perfusion associated with coronary artery disease.

The recession of ectopic activity accompanying the increased ventricular rate induced by catecholamines can also be interpreted. Epinephrine, norepinephrine, and isoproterenol may increase the frequency of idioventricular pacemakers, and

may also abbreviate the ventricular RP. The latter effect will be partly the result of a direct effect on the RP and partly a result of the increased frequency. In either case dispersion will be reduced. In a previous study it was shown that the degree of asynchrony of recovery in the ventricle is increased shortly after the beginning of an infusion of epinephrine (before uniform distribution is achieved) but the dispersion and the fibrillation threshold are significantly reduced when equilibrium is reached.[9] It is interesting that in one of the cases described by Linenthal and Zoll,[3] ectopic ventricular activity increased as the ventricular rate was accelerating at the start of an infusion but disappeared when the ventricular rate stabilized at a higher level.

In contrast with the effects of intravenously administered catecholamines, stimulation of the cardiac adrenergic nerves increases the degree of temporal dispersion at any given frequency and reduces the fibrillation threshold, an effect which is probably the result of nonuniform distribution of the adrenergic mediator.[9] This observation also has its clinical counterpart in one of the cases described by Linenthal and Zoll.[3] In this patient, ectopic activity was absent at rest but appeared as the heart rate accelerated with exercise; infusion of catecholamines restored a regular idioventricular rhythm.

Summary

Temporal dispersion of recovery of excitability, measured as the range of local refractory period durations at numerous sites on the atrial and ventricular surfaces, was found to be a direct function of the basic cycle length except at very rapid driving frequencies. In the atrium spontaneous ectopic activity followed early premature stimuli at slow but not at fast driving frequencies. In the ventricle, the fibrillation threshold was significantly lower at slow than at high basic frequencies. It was concluded that spontaneous closely coupled beats occurring at slow ventricular rates in A-V dissociation may result from asynchrony in the repolarization of adjacent excitable units.

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Dynamic left ventricular outflow obstruction experimentally induced

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In 1957 Brock described the syndrome of functional obstruction of the left ventricle. This entity was characterized by a systolic pressure gradient between the left ventricle and aorta, presumably resulting from muscular hypertrophy. The disease has since been described by various authors as pseudoaortic stenosis,[2] functional aortic stenosis,[3] functional systolic stenosis,[4] obstructive cardiomyopathy,[5] familial muscular subaortic stenosis,[6] "idiopathic hypertrophic subaortic stenosis,"[7] and muscular subaortic stenosis.[8] Numerous reports have confirmed this syndrome as being a specific entity with characteristic clinical, hemodynamic, and angiocardiographic features.[9-11]

In this report, obstruction of left ventricular outflow was experimentally produced in dogs by the intravenous administration of amphetamine. A significant gradient occurred in all 15 animals studied.

Methods

Fifteen healthy adult mongrel dogs (15 to 29.2 kilograms) were utilized.† None of the animals was premedicated or anesthetized except for local subcutaneous infiltration with 1 per cent lidocaine for purposes of cannulation. Each animal was placed on a specially designed restraining board which permitted excellent and painless immobilization. Handled gently, the animal was comfortable and relaxed. The surgery performed was essentially that of a standard catheterization procedure which in the usual clinical situation would require only local anesthesia.

Standard No. 7 NIH catheters were introduced into the left ventricular chamber and into either the ascending aorta or distal abdominal aorta via retrograde passage from the femoral vessels. Pressures were recorded on either a Sanborn No. 150 four-channel direct writing recorder using No. 267 B transducers, or an Electronics for Medicine Model DR-8 recorder using Statham P 23 DB strain gauges. Cineangiograms were obtained in 2 animals via left ventricular injections (Amplatz pressure injector) with 85 per cent Cardiografin (methylglucamine diatrizoate inj. U.S.P.,

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†The principles of laboratory animal care as promulgated by the National Society for Medical Research were observed.

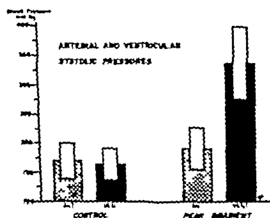


Fig. 1 The average arterial and ventricular systolic pressures in 15 experiments during the control period and at the time of the peak gradient. The insert represents one standard deviation from the mean. The slight disparity in the control pressures resulted from several experiments in which arterial pressures were obtained in the distal abdominal aorta.

Squibb) using a 9 inch Phillips image intensifier and a 35-mm Arriflex camera at a speed of 48 frames per second

After control determinations had been made amphetamine sulfate in a dosage of 10 mg per kilogram was administered intravenously over a period of 1 minute After the drug was given serial recordings were made until the animal died which generally occurred in less than 2 hours.

Results

All 15 animals developed a gradient between the left ventricle and aorta The maximum gradient attained in each experiment ranged from 80 to 220 mm Hg with the average for the group being 147 (S D 46) mm Hg Fig 1 depicts the average arterial and ventricular systolic pressures for the group during the control period

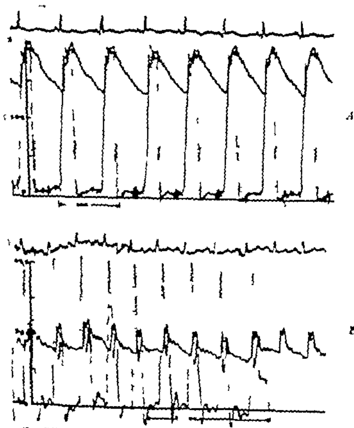


Fig 2 Experiment No. 84 A is the control recording prior to the administration of the amphetamine The arterial and left ventricular systolic pressures are nearly identical Paper speed is 50 mm. per second. *B* is a recording obtained 17 minutes after the amphetamine had been given Note the gradient of approximately 180 mm Hg between the left ventricle and ascending aorta. Paper speed is 100 mm per second.

and at the time of the peak gradient. The gradient usually developed within 5 to 15 minutes after the amphetamine had been administered. Fig. 2 is a representative recording demonstrating a gradient of 180 mm. Hg in Experiment No. 54. Withdrawal recordings from the left ventricle into the aorta were obtained in 7 of the animals and in each case a subvalvular chamber was demonstrated hemodynamically. Figs. 3, 4, and 5 are representative.

Cineangiograms demonstrated systolic narrowing of the left ventricular outflow tract, as well as a reduction in both the end-diastolic and end-systolic left ventricular chamber sizes. Fig. 6 shows selected frames from systole during three separate injections in Experiment No. 66.

Postmortem studies confined to the heart were performed in 5 animals. The findings were similar in each of the five hearts examined. The entire myocardium appeared to be contracted and foreshortened, thus giving an increase in the measurable thickness of the left ventricular wall and a decrease in cavitary volume. The most striking finding was relative obstruction of the aortic outflow tract by the contracted musculature of the left ventricle (Fig. 7). The muscle group implicated in this obstruction was the deep bulbospiral muscle, which extended from

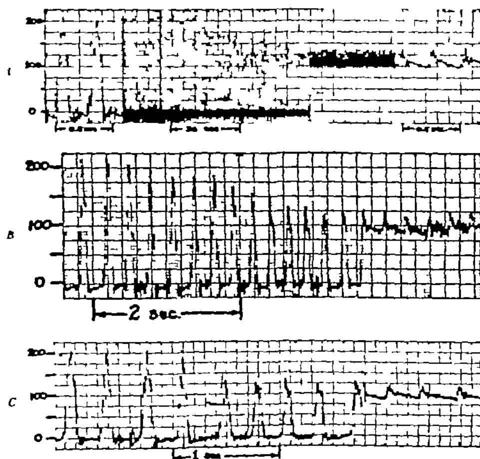


Fig. 3. Experiment No. 125 demonstrates pull-through recordings from the left ventricle into the aorta at varying times and paper speeds. A was obtained at a paper speed of 1 mm. per second with representative ventricular and arterial complexes at 50 mm. per second. Note the reduction of ventricular pressures as the catheter is removed from deep within the chamber. Time 33 minutes. B, Paper speed is 25 mm. per second, time 72 minutes. A gradient of 90 mm. Hg is present. C, Paper speed is 50 mm. per second, time 76 minutes. Note the reduced ventricular pressure as the catheter passes within the subvalvular chamber.

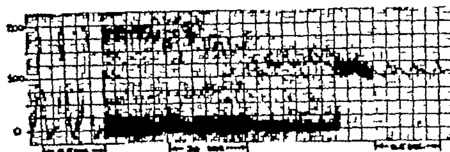


Fig. 4 Experiment No. 122. Pull-through recording at a paper speed of 1 mm. per second, time 43 minutes. A gradient of 75 mm. Hg is present.

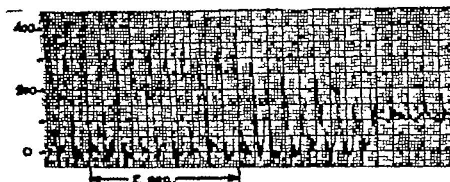


Fig. 5 Experiment No. 72. Pull-through recording at paper speed of 25 mm. per second, demonstrating a gradient of 180 mm. Hg. Time 38 minutes.

the anterior ventricular wall as a prominent firm cylindrical mass. This was most apparent above the superior papillary muscle of the mitral valve, extending into the region of the aortic outflow tract.

Discussion

Krasnow and his co-workers[11] previously reported the production of an aortic subvalvular gradient in dogs by the intravenous administration of isoproterenol. The gradient was attributed to the inotropic action of isoproterenol which was suspected of having induced "excessive circumferential contraction of the outflow tract compared with the rest of the ventricle." In the present study another sympathomimetic amine, amphetamine has been shown, in toxic doses, to produce a similar pressure gradient. Angiocardiographic studies and postmortem findings confirmed that the gradient was a result of obstruction of the outflow tract. The inotropic action of amphetamine is well known[12,14] and it is probable that this effect, directly or indirectly produced a relative narrowing of the left ventricular outlet.

The clinical disease idiopathic hypertrophic subaortic stenosis is thought to result from obstruction of left ventricular outflow produced during systole by the apposition of the hypertrophied musculature of the outflow tract and interventricular septum.[15] This is in contrast to other forms of left ventricular outflow obstruction as in aortic valvular stenosis or congenital subaortic stenosis, in which a discrete anatomic lesion is present. In idiopathic hypertrophic subaortic stenosis the obstruction relaxes during diastole and narrows during systole. At autopsy or during operation the hearts of patients with this disorder usually reveal diffuse



Fig. 6. Three series of angiocardiograms in Experiment No. 66. The frames are selected from early to late systole in each case and read from top to bottom. Series *A* was obtained during the control period, and Series *B* and *C* were obtained at 38 and 80 minutes, respectively, after the amphetamine had been given. Note particularly the reduction in chamber size, narrowing of the outflow tract, and apparent thickening of the ventricular wall which occurs in late systole in Series *B* and *C*.



Fig. 7. Gross sections of normal dog heart (*left*) and heart from Experiment No. 130 (*right*). The sections were made just superior to the anterior papillary muscle of the left ventricle in each case. The heart on the left weighed 152 grams, and that on the right weighed 135 grams. Note the apparent thickening of the left ventricular wall, narrowed ventricular chamber, and the muscular obstruction in the region of the outflow tract in the experimental heart.

hypertrophy of the left ventricle, with particular prominence of the septal musculature.[21] The etiology of the hypertrophied musculature is unknown.

The pharmacologic production of obstruction of left ventricular outflow, as was demonstrated in this study, illustrates the dynamic aspects of this entity. It is apparent that muscular hypertrophy is not a prerequisite for experimental outlet obstruction since, as in these experiments, the obstruction was produced in healthy animals within a relatively short period which precluded the development of muscular hypertrophy. Note, however, Fig. 7, in which the heart of the dog given amphetamine is markedly contracted so that the chamber is small and the ventricular wall appears to be thickened in comparison with the control heart. It is possible that true muscular hypertrophy would occur in the presence of outflow tract obstruction after a prolonged period of time. Although speculative, the possibility exists that the muscular hypertrophy of subaortic stenosis is a consequence rather than a cause of the disease. Since sympathomimetic amines have the capacity to reproduce many of the elements of idiopathic hypertrophic subaortic stenosis, it would appear that hyperactivity of the sympathetic nervous system, either via the cardiac sympathetic nerves or perhaps through a hormonal mechanism, might play a significant role in the etiology of this disease.

Summary

In 15 unanesthetized dogs the administration of toxic doses of amphetamine resulted in the prompt appearance of a high degree of subvalvular and left ventricular outflow tract obstruction. Hemodynamic, angiocardiographic, and postmortem findings revealed striking similarities between the experimental model and the clinical disease, idiopathic hypertrophic subaortic stenosis.

The author sincerely appreciate the assistance of Dr Michael W Hannegan in ev l ating the postmortem findings nd Dr Eliot M Rapaport for guidance in the study

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Mitral regurgitation and intramyocardial injection resulting from left heart catheterization

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The investigation of mitral valve function involves the determination of pressures and gradients and the performance of angiography during left heart catheterization. Two of the commonly employed methods are the transseptal and the retrograde aortic approaches. One of the hazards of either technique is injection of contrast material into the myocardium. Also with either method mitral regurgitation may occur during the injection of contrast material into the left ventricle, and the question then arises whether this represents true mitral valve insufficiency or whether it has been induced by the procedure itself. With the transseptal approach the position of the catheter through the mitral valve may displace a leaflet, whereas a retrograde catheter passed through the aortic valve into the left ventricle may impinge upon the chordae tendineae and produce mitral insufficiency. Also, with either technique premature ventricular contractions induced by the catheter or by injection of the contrast material may result in mitral regurgitation. These considerations led to an investigation of the incidence of false mitral regurgitation and intramyocardial injection during transseptal and retrograde aortic injections in dogs with normal mitral valves.

Methods

Mongrel dogs weighing 20 to 30 pounds were anesthetized with intravenous pentobarbital. A No. 7 Lehman catheter was passed retrogradely from the femoral artery to the left ventricle and the child sized Brockenbrough transseptal catheter was threaded from the femoral vein to the left atrium and left ventricle. The contrast material employed was 15 ml. of 66.8 per cent sodium iothalamate† injected under 90 pounds of pressure in 1.0 to 1.5 seconds. Cineangiograms were recorded in the left lateral position on 16-mm. Kodak Linagraph Shellburst Film at 30

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frames per second using 85 kv and 20 Ma A simultaneous electrocardiogram timed the injection period and recorded any premature ventricular contractions

In each dog at least three injections were carried out as follows (1) Transseptal catheter in the left ventricle retrograde catheter *in the left ventricle injection through the transseptal* catheter (2) Transseptal catheter in the left ventricle retrograde catheter in the left ventricle *injection through the retrograde* catheter (3) Transseptal catheter in the left atrium retrograde catheter in the left ventricle *injection through the retrograde* catheter In some experiments more than one injection was made under the same conditions especially if an intramyocardial injection or frequent premature ventricular contractions occurred

Mitral regurgitation detected by appearance of the contrast material in the left atrium was graded as slight (1+) if only a puff of contrast material appeared in this location as significant (2+ and 3+) if it was easily seen in the left atrium and as massive (4+) if the left atrium was completely opacified

The extent of any observed intramyocardial injection was classified as slight or moderate if it was small in amount, if the cardiovascular disturbances were brief and if the contrast material had completely disappeared from the myocardium in 10 minutes. The intramyocardial injection was considered to be extensive if approximately half the contrast material appeared to be injected into the myocardium and the injection was followed by prolonged hypotension and tachycardia

Results

The results are tabulated in Table I Ten dogs were studied and 4 or 5 injections were made in each animal

A Premature ventricular contractions Premature contractions were slightly more frequent with injections through the transseptal catheter (14/21—Table I Section 1) than with retrograde injections and mitral regurgitation was more extensive Injection of contrast material through the retrograde catheter resulted in ventricular premature contractions in about half of the injections (11/24) whether the transseptal catheter

Table I

1 Transseptal catheter in left ventricle retrograde catheter in left ventricle *injection through transseptal catheter*
   a) Extra systoles and significant regurgitation—14 cases
   b) No extra systoles and slight regurgitation—6 cases
   c) No extra systoles and no regurgitation—1 case

2. Transseptal catheter in left ventricle retrograde catheter in left ventricle *injection through retrograde catheter*
   a) Extra systoles and significant regurgitation—3 cases
   b) Extra systoles and slight regurgitation—3 cases
   c) No extra systoles and slight regurgitation—3 cases
   d) No extra systoles and no regurgitation—5 cases

3 Transseptal catheter in left atrium retrograde catheter in left ventricle *injection through retrograde catheter*
   a) Extra systoles and slight regurgitation—3 cases
   b) Extra systoles and no regurgitation—2 cases
   c) No extra systoles and no regurgitation—5 cases

4 Intramyocardial injection
   a) Injection through retrograde catheter—0/24 cases
   b) Injection through transseptal catheter
      i) Minimal to moderate—4/21 cases
      ii) Extensive—3/21 cases

was in the left ventricle or withdrawn to the left atrium (Table I Sections 2 and 3)

B Mitral regurgitation Injection of contrast material through the transseptal catheter in the left ventricle was associated with mitral regurgitation in 20 of 21 injections (Table I Section 1) Even in the absence of premature ventricular contractions slight regurgitation occurred in 6 of 7 injections (Fig 1) whereas in all 14 injections accompanied by premature contractions the regurgitation was classified as 2+ or 3+ (Fig 2)

The incidence and the degree of mitral regurgitation associated with injection of contrast material through the retrograde catheter was increased by the presence of the transseptal catheter through the mitral valve (Table I Section 2) Under these conditions mitral regurgitation occurred



Fig. 1. Slight regurgitation during injection through the transeptal catheter in the absence of premature ventricular contractions.



Fig. 2. Significant regurgitation during injection through the transeptal catheter in the presence of premature ventricular contractions.

in 9 of 14 retrograde injections. Eight of the 14 were not accompanied by ventricular premature contractions, but nevertheless, mitral regurgitation occurred in 3 of these 8 (Fig. 3).

When the transseptal catheter was in the left atrium rather than through the mitral valve (Table I, Section 3), slight mitral regurgitation occurred in only 3 of 10 retrograde injections, was never significant in amount, and was seen only when the injection was accompanied by premature contractions. Mitral regurgitation did not occur with retrograde injection in the absence of premature contractions (5 cases), and in 2 of the 5 cases in which ventricular premature contractions did occur during a retrograde injection, mitral regurgitation did not result (Fig. 4).

C. Intramyocardial injection. Intramyocardial injection of the contrast material was not seen with retrograde injection (0/24), but occurred in 7 of 21 injections through the transseptal catheter in the left ventricle (Fig. 5). This was minimal to moderate in degree in 4 cases and extensive in 3, and was always accompanied by massive mitral regurgitation and ventricular premature contractions (Table I, Section 4).

Discussion

One can conclude from these observations that the injection of contrast material through a transseptal catheter in the left ventricle is associated with a higher incidence of premature ventricular contractions and intramyocardial injections than injection through a retrograde aortic catheter. In fact, whereas there was a 33 per cent incidence of intramyocardial injection with the transseptal approach, this complication did not occur in this series when the injection was made through a retrograde catheter. In each technique, the catheter employed had both end and side holes, and the same pressure and volume of contrast material were used. The higher incidence of intramyocardial injection and ventricular extrasystoles with the transseptal approach was probably related to fixation of the catheter by the atrial septum so that the bolus of contrast material was concentrated in one area. The angle of entrance of the catheter into the left



Fig 3 Sign fic t regurgit tion during jection through the retrograde theter in th b of premature ontract n but with the tr septal catheter through the mitr l l



Fig 4 Absenc of regurgit tion during injection through the retrograd theter despit the re urrence of premature ontractions (tr nsseptal theter n left atrium)

ventricle in the transseptal route may also have predisposed to intramyocardial injection in some cases, because the catheter was directed toward the wall of the ventricle and had less than maximum maneuverability within the ventricular cavity Both of these factors may have been accentuated by the small size of the experimental animal (20 to 30 pounds) although the techniques and equipment used were those employed in the study of human infants in this laboratory

Although it did not lead to immediate death even in a dog that received two insults in the same experiment, intramyocardial injection did produce massive hemorrhage in the myocardium of one dog which was demonstrated post mortem Intramyocardial injections during retrograde cineangiography have occurred in human beings, and myocardial infarction has been reported [1]

Although the small size of the experimental animal and the presence of side holes in the catheter might have been



Fig 5 Intramyocardial injection occurring through the transseptal catheter in the left ventricle

factors that led to opacification of the left atrium during transseptal catheterization the authors believe that the high incidence of mitral insufficiency that occurred when contrast material was injected into the left ventricle through a transseptal catheter was probably caused by interference with closure of the mitral valve. This conclusion was supported by the demonstration that injection of contrast material into the left ventricle through a retrograde aortic catheter was accompanied by a higher incidence of mitral insufficiency when the transseptal catheter was in the left ventricle than when it was in the left atrium. The absence of mitral regurgitation in left ventricular angiocardiographic studies in which the retrograde or subxiphoid approach has been employed clinically further suggests that the transseptal catheter is itself important in causing this phenomenon.[2-]

Ventricular premature contractions were shown by Rodbard and Williams[3] to be important in the enhancement of mitral regurgitation. These authors point out that both the celerity and the strength of ventricular contraction are factors in determining the degree of mitral regurgitation. The diminution of these parameters during premature ventricular contraction would enhance the mitral insufficiency produced by other factors, such as the mechanical effect of the catheter through the mitral valve. At the same time, the increased incidence of premature contractions during intraventricular injections through a transseptal catheter would provide more opportunities for an error in interpretation.

The occurrence of false mitral regurgitation during transseptal left ventricular cineangiography in normal dogs raises the question of the diagnostic value of this procedure in the assessment of the function of the mitral valve in human beings. It has been our impression and that of other workers that there is also a high incidence of fictitious mitral regurgitation in human beings studied by the transseptal technique. Although this has been stated to be slight and of little consequence,[1] the results of the present study would seem to contradict this view. The high incidence of significant mitral regurgitation during transseptal angiography in normal dogs makes the observation of even moderate degrees of regurgitation in human beings of doubtful significance, especially if the injection is accompanied by premature ventricular contractions. The occurrence of mild regurgitation during retrograde aortic study is also of doubtful significance when the injection is accompanied by premature contractions. These facts could not only lead to an erroneous diagnosis of mitral regurgitation in patients suspected of having left-sided valvular disease but could also result in the unfounded suspicion of an ostium primum defect with mitral insufficiency in a patient who has a simple ostium secundum atrial septal defect.

Summary

The incidence of mitral regurgitation and intramyocardial injection of contrast material during left heart catheterization in normal dogs has been investigated, comparing the transseptal with the retrograde aortic approach.

A transseptal catheter passed through the mitral valve into the left ventricle almost always caused some regurgitation during injection of contrast material, even in the absence of premature ventricular contractions. There was a 33 per cent incidence of intramyocardial injection when the transseptal catheter was employed.

Retrograde aortic catheterization was associated at times with minimal mitral regurgitation when premature ventricular contractions occurred during injection, but significant mitral regurgitation was never produced. In the absence of premature contractions, regurgitation did not occur. Intramyocardial injection of contrast material was not observed in this series when the retrograde aortic catheter was employed.

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A modification of the Dotter-Lukas catheter

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There are a variety of techniques in use for assessing the pulmonary function of patients being subjected to resectional pulmonary surgery. It is not the purpose of this communication to discuss the merits of any of these. However, 2 years ago bronchospirometry was abandoned by this laboratory in favor of balloon occlusion of the right or left pulmonary artery. The results of the findings in the patients catheterized during the past 2 years will be the subject of a subsequent report. However, because of the high incidence of cardiac perforations sustained with this procedure, it seemed to be worth while to report on the use of a safer and more effective balloon catheter.

By means of a standard Dotter-Lukas catheter* (Fig. 1,*A*), 16 patients were catheterized for the purpose of occluding the right or left main pulmonary artery. Out of this total group of patients, the procedure in 3 was terminated because of perforation of the right atrium. Hemorrhage into the pericardium was not sufficiently severe in any of these to require thoracotomy, nor did it produce any significant morbidity. In each case the entry of the tip of the catheter into the pericardial sac was confirmed by fluoroscopy as well as by the withdrawal of serous or serosanguineous material from the catheter.

Hundreds of right heart catheterizations have been performed in this laboratory by the same operators, without the occurrence of any perforations. The Dotter-Lukas catheter is a No. 9 French catheter, as is the standard right heart catheter in use in this laboratory (Fig. 1,*B*). Neither the standard catheter, which is routinely used even in children as young as 6 years, nor the Dotter-Lukas catheter is autoclaved prior to use. Sterilization is achieved by soaking in Detergicide. This tends to increase the pliability of the catheter, in contradistinction to autoclaving, which tends to stiffen it. Despite the fact that both catheters are made of the same material and are of the same external diameter and both are handled in the same fashion, the subjective impression was that the Dotter-Lukas catheter tended to be more rigid at its distal end. In addition, its distal end was somewhat square in shape rather than being rounded. For both of these reasons, the high incidence of perforations was thought to be due to the catheter itself.

In order to avoid future entries into the pericardium, the catheter illustrated in Fig. 1,*C* was designed. This catheter is similar to the Dotter-Lukas catheter, with the exception of the terminal 4 cm, which is No. 4 French rather than No. 9. This

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*All catheters described here were made for us by the United States Catheter and Instrument Company, Glens Falls, N. Y.



Fig 1 Various cardiac catheters See text

modification provides considerable pliability to the tip, and in the past 28 catheterizations no perforations have occurred

The catheter was further modified by altering the balloon The balloon on the standard Dotter Lukas catheter can be inflated only to a diameter of 2.2 cm Attempts at further inflation of the balloon result in an increase in size only along its long axis and not in its diameter Since the average diameter of the adult right main pulmonary artery is 2 4 cm the balloon therefore, cannot be inflated to a diameter sufficiently large to occlude the right main pulmonary artery in the average adult The balloon as modified is capable of occluding the right or left main pulmonary artery in adults since, when inflated its diameter is 3 2 cm

One final modification of the catheter was the addition of a platinum electrode at its distal end (Fig 1 D) This is an added safety precaution which permits the rapid detection of impingement of the tip against the endocardium by the display of a current of injury on the continuously monitored intracardiac electrocardiogram This electrode also permits assurance that the balloon is occlusive which can be ascertained by the inhalation of hydrogen gas by the patient, or the injection of ascorbic acid through the proximal lumen The appearance of either substance at the electrode indicates that the balloon is not completely occluding the pulmonary artery in question.

One potential although not serious, drawback with this catheter should be pointed out. Because of the very proximal position of the balloon deep penetration into the affected lung must be achieved in order to bring the balloon into the pulmonary artery to be occluded If this is not done the balloon will remain in the ventricle or in the main pulmonary artery In one instance presumably because of distortion of the pulmonary vascular bed by a tumor near the hilum the catheter could not be advanced sufficiently far out to permit entry of the balloon into the pulmonary artery in question.

Summary

Because of a high incidence of cardiac perforations with the Dotter Lukas catheter a modification of the Dotter Lukas triple-lumen balloon catheter is presented The advantages include a more flexible tip a larger balloon and a platinum electrode to warn of impingement against the endocardium during passage of the catheter as well as to insure complete occlusion by the balloon by the hydrogen-gas or ascorbic acid technique.

The effects of a beta-adrenergic blocking agent, pronethalol, on digitalis-induced ventricular arrhythmias

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The recent availability of beta-adrenergic blocking agents has stimulated new inquiries into the mechanism of production of digitalis-induced arrhythmias. Early work suggested that one could modify arrhythmias due to digitalis by either surgical or pharmacologic adrenergic blockade.[1] Although dichloroisoproterenol (DCI) was able to reverse digitalis-induced arrhythmias and produced effective beta-adrenergic blockade,[2] this compound also had significant sympathomimetic activity. With the introduction of pronethalol and related compounds it has become possible to obtain effective beta-adrenergic blockade[3] with little[4] or no sympathomimetic effect. The ability of DCI[5] and pronethalol[4,6] to modify ventricular arrhythmias due to digitalis has been noted previously. In order to investigate further the mechanism of this effect, the following study was undertaken.

Methods

Mongrel dogs were anesthetized with intravenous pentobarbital and intubated with a cuffed endotracheal tube which was attached to a Harvard respiratory pump. Ventilation with room air was maintained at 170 ml. per minute per kilogram of body weight. Small supplementary intravenous doses of pentobarbital were given as needed. Indwelling catheters were placed in the femoral artery and vein. Arterial pressure was measured using a Model P23AA Statham transducer and inscribed on a direct-writing Sanborn recorder. Simultaneous recordings were made of a standard lead electrocardiogram, femoral arterial pressure, and its first derivative (dp/dt). The latter measurement was made using an electronic differentiating circuit.

The dogs studied were divided into four groups: (a) 8 control animals (1C-8C)

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without pretreatment (b) 5 animals (1R-5R) pretreated with intraperitoneal reserpine (Serpasil) 0.5 mg. per kilogram per day for 2 days (evidence that a significant reserpine effect had occurred included weakness, meiosis, and diarrhea) (c) 5 animals (1G-5G) pretreated with intraperitoneal guanethidine sulfate 2.5 mg. per kilogram per day for 2 consecutive days and (d) a final group of 6 animals (1P-6P) pretreated intravenously with pronethalol 2.5 mg. per kilogram 10 to 20 minutes before the start of an infusion of acetylstrophanthidin. This period of 10 to 20 minutes was required for mean arterial pressure and heart rate to return to control levels.

In order to test the adequacy of catecholamine depletion 2 control dogs, 2 pretreated with reserpine and 2 pretreated with guanethidine in the doses specified above were challenged with intravenous tyramine, 0.05 mg. per kilogram.

In each experiment acetylstrophanthidin was infused into the femoral vein at a constant rate of 0.1 mg. per minute. At the first evidence of a ventricular arrhythmia the infusion was discontinued and the total dose of acetylstrophanthidin given was recorded.

Several animals in the control group and in each of the pretreated groups were given pronethalol after the appearance of the ventricular arrhythmia, in order to assess the ability of this compound to reverse the arrhythmia. Five minutes after the appearance of the toxic rhythm and discontinuation of the infusion of acetylstrophanthidin pronethalol was administered intravenously at a rate of 1.0 mg. per kilogram per minute to a total dose of 2.5 mg. per kilogram of body weight. The time required for reversion to a stable sinus rhythm was noted. Arterial pH, pO_2, pCO_2, and venous Na, K, CO_2, Cl and Ca were measured at intervals throughout the experiments.

Results

Arterial oxygen saturation, pO_2, pCO_2, and pH and venous Na, K, CO_2, Cl and Ca did not change significantly during the course of these experiments.

The heart rates and arterial blood pressures of control dogs and of dogs pretreated with reserpine, pronethalol and guanethidine are shown in Table I. Animals pretreated with reserpine demonstrated both bradycardia and hypotension. Although animals *pretreated* with pronethalol showed an *initial* decrease in heart rate and blood pressure, their mean arterial pressure and heart rate returned to control levels within 10 to 20 minutes. Pretreatment with guanethidine resulted in hypertension and bradycardia.

The amount of acetylstrophanthidin necessary to produce a ventricular arrhythmia in the various test groups is shown in Table II. Although dogs pretreated with reserpine tolerated a slightly larger dose

Table I. Heart rates and blood pressures of the dogs in each of the experimental groups

No.	HR	BP	Mean BP
Control			
1C	150		—
2C	135	—	—
3C	140	124/92	103
4C	110	125/90	105
5C	150	144/90	100
6C	98	148/80	100
7C	115	135/75	90
8C	160	115/75	85
Mean	132	132/84	97
Reserpine pretreatment			
1R	65	125/85	100
2R	105	110/80	85
3R	53	155/90	105
4R	85	100/65	75
5R	65	90/63	73
Mean	75	116/77	88
Pronethalol pretreatment			
1P	120	140/65	90
2P	115	100/84	76
3P	96	150/75	100
4P	100	145/100	120
5P	150	165/115	132
6P	130	105/90	93
Mean	118	134/88	102
Guanethidine pretreatment			
1G	112	95/70	80
2G	130	200/150	160
3G	150	190/140	160
4G	84	180/130	150
5G	90	200/130	180
Mean	113	173/124	146

Table II. Dose of acetylstrophanthidin required to produce a ventricular arrhythmia

Control dogs	*Dogs pretreated with pronethalol*	*Dogs pretreated with reserpine*	*Dogs pretreated with guanethidine*
1C 82 µg/kg	1P 178 µg/kg	1R 109 µg/kg	1G 106 µg/kg
2C 69	2P 137	2R 150	2G 125
3C 144	3P 53	3R 127	3G 112
4C 113	4P 77	4R 95	4G 111
5C 88	5P 85	5R 117	5G 82
6C 71	6P 100		
7C 56			
8C 95			
Mean ± S.E.M.* 90 ± 10 µg/kg	105 ± 18 µg/kg	120 ± 9 µg/kg†	107 ± 16 µg/kg

*Standard error of the mean.
†.025 < p < .05, compared to Control.

Table III. Time required for reversion of digitalis-induced arrhythmias

Control animals (Spontaneous reversion)	*Pretreatment with pronethalol (Spontaneous reversion)*	*Control animal (Pronethalol after VT)*	*Pretreatment with reserpine (Pronethalol after VT)*	*Pretreatment with guanethidine (Pronethalol after VT)*
1C 28 min.	1P 19 min.	5C 1 min	2R 2 min.	1G 1 min
2C 17	2P 17	6C 2	3R 2	2G 1
3C 18	5P 19	7C 1	4R 2	3G 2.5
4C> 27	6P> 20	8C 3	5R 2.5	
> 20 min	> 20 min.	1.8 min.	2 min	1.5 min.

of acetylstrophanthidin than did controls the dose was not significantly different among the other groups. The time required for the animals in each group to recover from the abnormal rhythm is shown in Table III. Spontaneous recovery occurred in control dogs in about 20 minutes. *Pretreatment* with pronethalol did not alter the duration of the spontaneous recovery period. In contrast, after the ventricular arrhythmia had become established treatment with pronethalol resulted in almost immediate reversion to a normal sinus mechanism. Pronethalol was equally effective in reversing the ventricular arrhythmia in both reserpine pretreated and guanethidine-pretreated animals. These pretreated animals had received amounts of these drugs reported to produce substantial depletion of catecholamines[9] and in addition in comparison with control dogs, their response to intravenous tyramine was markedly reduced (Fig. 1).

The dose of pronethalol required to acutely reverse the digitalis-induced arrhythmias in these experiments was 2.5 mg. per kilogram. This dose resulted in an 80 per cent inhibition of the increase in dp/dt brought about by intravenous isoproterenol, 0.5 µGm. Yet only 0.25 mg. per kilogram of pronethalol was needed to produce equally effective although transient, beta-adrenergic blockade.

The ability of pronethalol to reverse a ventricular tachycardia due to acetylstrophanthidin is shown in Fig. 2. During the infusion of acetylstrophanthidin progressive S-T segment and T wave changes

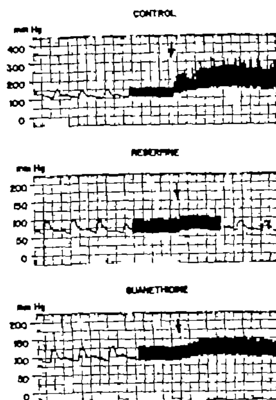


Fig. 1. Blood pressure response to intravenous administration of tyramine [illegible] control dog, [illegible] dog pretreated with reserpine, and one pretreated with guanethidine. In each case 0.05 mg. per kilogram of tyramine was given at the arrow. The control animal responded with a dramatic increase in blood pressure, but the response of the pretreated animals was markedly reduced. Note that the reserpine and guanethidine tracings were recorded at twice the sensitivity of the control.

were observed. With the onset of ventricular tachycardia, the infusion was discontinued, and after 5 minutes pronethalol was infused. Reversion to sinus rhythm occurred within 1 minute.

Discussion

Although some investigators have found a relationship between cardiac sympathetic receptors and digitalis-induced arrhythmias,[11] others have failed to demonstrate this relationship.[12] Méndez, Aceves, and Méndez[1] demonstrated an increase in the lethal dose of acetyldigitoxin in the sympathectomized adrenalectomized dog. They also noted that the fatal arrhythmia in these animals was ventricular arrest rather than ventricular fibrillation. Lucchesi and Hardman[4] reported the effectiveness of dichloroisoproterenol (DCI) in reversing arrhythmias due to digitalis, but also noted the same effect with analogues of DCI that had no beta adrenergic blocking activity. These authors concluded that the antiarrhythmic effect of DCI was independent of its ability to block beta adrenergic receptors.[5]

In the present study, pronethalol was found to reverse effectively digitalis-induced arrhythmias in the anesthetized dog. Reversion occurred even when these animals had been pretreated with doses of reserpine or guanethidine which result in marked depletion of myocardial cathechol amines.[11] Furthermore, these drugs had no significant effect on the time required for pronethalol to reverse the arrhythmia. In addition, as little as 0.25 mg. per kilogram of pronethalol resulted in effective although transient beta blockade but had no significant antiarrhythmic effect. These observations suggest that pronethalol, like DCI, has an antiarrhythmic effect that is independent of its beta adrenergic blocking action. Furthermore, the antiarrhythmic effect of pronethalol persisted for a much shorter period than did its beta blocking effect. The dose of pronethalol that immediately abolished digitalis-induced ventricular tachycardia failed to prevent the appearance of the arrhythmia when given 20 minutes before acetylstrophanthidin was infused. Yet effective beta-adrenergic blockade persisted for a full hour after this same dose.

It is recognized that the rate of rise of the peripheral arterial pressure (dp/dt) is not an accurate reflection of dp/dt in the left ventricle. However, for comparative purposes, the response of arterial dp/dt to isoproterenol before and after pronethalol is thought to be a useful measure of beta adrenergic blockade.

The dogs pretreated with reserpine tolerated a slightly larger dose of acetylstrophanthidin than did the controls ($0.025 < p < 0.05$). Other investigators have found varying effects of reserpinization upon the dose of acetylstrophanthidin required to induce ventricular tachycardia. Some have found no increase in tolerance to digitalis by reserpine therapy,[13] whereas others

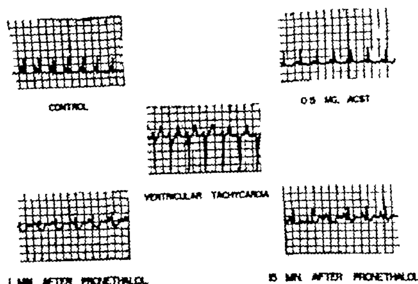


Fig. 2. Conversion of digitalis-induced ventricular tachycardia to sinus rhythm by pronethalol. Acetylstrophanthidin (ACST), 0.5 mg. produced ST-T wave changes. Ventricular tachycardia developed after 113 μg per kilogram of ACST had been given. The lower left-hand panel shows the sinus mechanism that appeared within 2 minutes after pronethalol had been given. This sinus rhythm was then stable for the duration of the experiment, as shown in the lower right-hand panel.

have noted a significant increase in tolerance to digitalis in animals treated with reserpine.[15,23]

In the present study, dogs pretreated with pronethalol were not protected against acetylstrophanthidin-induced arrhythmias. This observation is in substantial agreement with the recently reported findings of Somani and Lum.[4] The findings of others, using different species, have been somewhat different. Vaughan-Williams and Sekiya[5] found that guinea pigs pretreated with pronethalol 5 to 15 mg. per kilogram tolerated larger amounts of ouabain before developing ventricular tachycardia and dying. These workers also suggested that pronethalol resembled quinidine in many respects.[5] It is well known that acetylstrophanthidin causes an efflux of potassium from myocardial cells, and Taylor, Johnston, and Jose have found that in dogs pronethalol, like quinidine and procaine amide,[17,18] acts to reduce this loss of potassium from cardiac muscle.[1] Whether this is the fundamental manner in which pronethalol reverses arrhythmias due to digitalis remains to be determined.

On the basis of the present studies it would seem to be reasonable to investigate analogues of pronethalol in an effort to find a compound with long-term antiarrhythmic activity but without any beta adrenergic blocking properties.

Summary

The ability of pronethalol, a beta adrenergic blocking agent, to protect against and to reverse digitalis-induced ventricular arrhythmias has been studied.

Pronethalol quickly and permanently reverses arrhythmias due to acetylstrophanthidin. The dose of pronethalol required to restore promptly a sinus mechanism was far in excess of that which produced acute beta adrenergic blockade. Pretreatment with pronethalol in a dose that yielded effective and prolonged beta-adrenergic blockade, failed to protect dogs against acetylstrophanthidin-induced arrhythmias in these experiments. Pretreatment with reserpine or guanethidine did not alter the ability of pronethalol to restore a sinus mechanism.

It is concluded that the ability of pronethalol to reverse ventricular arrhythmias due to digitalis is not related to its action as an adrenergic blocking agent, but may be a function of its quinidine-like effect.

Addendum

Since this paper was submitted for publication Lucchesi[20] has reported that the *dextro*isomer of pronethalol effectively reverses digitalis-induced cardiac arrhythmias, although it has only one fortieth of the beta-adrenergic blocking activity of the *levo*isomer

We gr tefully acknowledge the kindness of Dr Alex Sahagun-Edwards, Ayerst Laboratories who provided liberal supply of pronethalol (Alderlin) for use in this tudy A upply of acetylstrophanthidin wa generously provided by the Eli Lilly Company W are also indebted to Dr I ul N Yu for his helpful suggestions nd review of the ma u script nd t Mrs Bonnie Sollie and Miss Sharon Frederick for secretarial assistance.

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The exercise phonocardiogram in mitral stenosis

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Prolongation of the Q-1 interval beyond 0.07 second is generally considered to be indicative of hemodynamically significant mitral stenosis, as is shortening of the 2-O.S. interval to 0.07 second or less but a linear relationship does not exist.[1] The variation in these intervals is dependent on the magnitude of elevation of left atrial pressure. In many cases of significant mitral stenosis the left atrial pressure is not elevated at rest, but becomes elevated with exercise. In these cases the Q-1 and 2-O.S. intervals would be expected to be normal at rest but abnormal with exercise. If the mitral stenosis is hemodynamically insignificant and the left atrial pressure does not show an appreciable rise with exercise, the Q-1 and 2-O.S. intervals would be expected to be normal both before and after exercise. Therefore the performance of exercise should enhance the usefulness of the phonocardiogram in evaluating the severity of mitral stenosis.

Methods and materials

Forty-three patients with mitral stenosis who were evaluated at the University of Kansas Medical Center were selected for this study. Patients with systemic hypertension and other hemodynamically significant valvular lesions were excluded from the study. Patients who were severely symptomatic and could not tolerate exercise were also excluded. All patients had routine histories and physical examinations, chest x-ray films, and twelve-lead electrocardiograms. The Sanborn Twin-Beam phonocardiograph was used to record a phonocardiogram with venous pulse tracing, carotid pulse tracing, apexcardiogram, and electrocardiogram as reference tracings. At the completion of the routine recording of the phonocardiogram another sound tracing was obtained from the precordial area where the opening snap was optimally recorded. This area was marked and postexercise recordings were obtained from the same area at the same amplification. An electrocardiogram was used for a reference tracing.

Each patient was required to perform a single Master two-step test in 1½ minutes as determined from standard Master tables. A simultaneous sound tracing and electrocardiogram were obtained at 1, 3, 5, and 10 minutes after exercise. The Q-1 and 2-O.S. intervals were determined from the resting tracing and at each time interval

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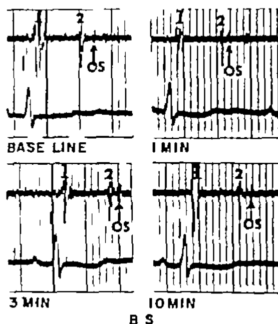


Fig. 1. A positive exercise phonocardiogram showing a 2-O.S. interval of 0.06 second at 3 minutes after exercise. The 2-O.S. interval was measured from the first major negative deflection of the aortic component of the second sound to the major negative component of the opening snap.

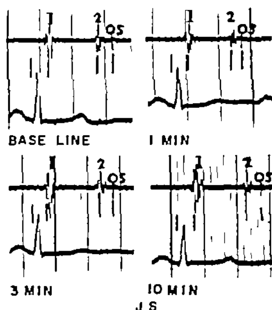


Fig. 2. A negative exercise phonocardiogram showing a 2-O.S. interval of 0.05 second at 3 minutes after exercise.

after exercise. No correction was made for heart rate. When atrial fibrillation was present, the 2-O.S. interval was measured from complexes which followed a diastolic interval most closely approximating a heart rate of 75. The response to the exercise test was considered to be positive if the 2-O.S. interval was 0.07 second or less at 3 minutes after exercise (Fig. 1) and if the following additional criteria were fulfilled: (1) the heart rate was between 60 and 100 at 3 minutes after exercise, (2) there was no evidence of significant associated aortic stenosis, aortic insufficiency, or mitral insufficiency, (3) the patient's systolic blood pressure was between 100 and 140 mm. Hg. Fig. 2 shows a negative test.

During the course of the study, mitral valvotomy was performed on 18 patients. In each instance the preoperative and postoperative mitral valve areas were estimated by the surgeon. Seven patients were tested both before and after mitral valvotomy. An additional 11 patients underwent right and left heart catheterization. Left heart catheterization was performed by the transseptal and retrograde aortic techniques. Cardiac output was determined by the direct Fick method[7] and mitral valve area was calculated by the technique of Gorlin and Gorlin. Fourteen patients have been evaluated clinically but have not undergone cardiac catheterization or heart surgery.

According to Gorlin,[8] the mitral stenosis was considered to be mild if the valve area calculated at catheterization or estimated at operation was greater than 2.0 cm^2, moderate if the valve area was 1.1 to 2.0 cm^2, and severe if the valve area was 1.0 cm^2 or less.

Results

2-O.S. interval. Measurement of the postexercise 2-O.S. interval was a useful parameter for assessing the severity of the mitral stenosis. Of the 29 patients who had mitral valvotomy or cardiac catheterization, there were 8 with severe stenosis, 12 with moderate stenosis, and 9 with mild stenosis. All of the 8 patients with severe stenosis had positive exercise tests.

Of the 12 patients with moderate stenosis, 10 had positive tests. In one of the

patients with a negative test the determination of cardiac output at catheterization was extremely low. Consequently the calculated mitral valve area was small. This may have been an erroneous measurement. In the other patient with the negative test the electrocardiogram showed a complete left bundle branch block. Her left ventricular pressure tracing showed a prolongation of the phase of isometric relaxation (Fig. 3). This delay in relaxation may have been secondary to the aberrant depolarization and was of sufficient duration to account for the negative test. Although a delay in the isometric relaxation is occasionally seen in mitral stenosis, this usually occurs at a lower pressure (at the peak of the v wave of the left atrial trace).

Of the 9 patients who had mild stenosis, all had negative tests. One of these patients was restudied 2 years later when she became more symptomatic. Her exercise test was positive and her mitral valve area was calculated to be 1.07 cm.² at catheterization.

Four of the patients with severe stenosis had positive tests preoperatively and negative tests postoperatively. The valve area was increased to at least 3.5 cm.² in each case. Three patients continued to have positive tests postoperatively in spite of the fact that the surgeon thought that an adequate valvotomy had been performed. The patients are asymptomatic and have not been restudied.

A scattergraph (Fig. 4) shows the distribution of patients with severe, moderate, and mild mitral stenosis in relation to their 2-O.S. intervals at 3 minutes after exercise. Seventeen of 20 patients with moderate or severe stenosis had 2-O.S. intervals of 0.07 second or less, whereas all the patients with mild stenosis had 2-O.S. intervals of 0.08 second or more.

Fourteen patients have not been operated upon or catheterized because they either have minimal symptoms or have refused recommended studies. Six had positive tests and 8 had negative tests.

A 2-O.S. interval of 0.07 second or less at rest is usually considered to be indicative of hemodynamically significant mitral stenosis. Only 8 of the 24 patients with positive exercise tests had resting 2-O.S. intervals of 0.07 second or less. Had the



Fig. 3. The left ventricular pressure tracing in the patient with complete left bundle branch block shows a prolongation of the phase of isometric relaxation (notching on the descending limb) at a pressure of 50 to 60 mm. Hg. The left atrial pressure tracing is superimposed upon the left ventricular tracing. *LV*, Left ventricle. *LA*, Left atrium.

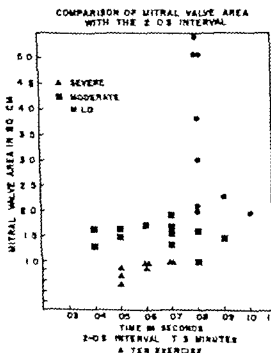


Fig. 4. Comparison of mitral valve area with the 2-O.S. interval.

resting 2-O.S interval been used as the sole criterion for assessing the severity of the mitral stenosis 65 per cent of our patients with significant lesions would have been inappropriately evaluated. Therefore the exercise test appears to enhance the accuracy of the 2-O.S interval in assessing the severity of mitral stenosis.

Q-1 interval. The Q-1 interval was found to be of no value in predicting the severity of the mitral stenosis. A resting Q-1 interval greater than 0.07 second was found in 29 of the 43 patients but was of no value in differentiating those with significant stenosis. Changes in the Q-1 interval after exercise did not correlate with the severity of the lesion. The failure of the Q-1 interval to correlate with the size of the mitral valve has been noted by others.[4] Since the end-diastolic pressure gradient across the mitral valve is smaller than the early diastolic gradient and since the period of isometric contraction is shorter than the period of isometric relaxation the change in duration of the Q-1 interval associated with elevations in left atrial pressure is less marked than the change in the 2-O.S interval.

Discussion

The phonocardiogram has been a useful tool in the evaluation of patients with mitral stenosis. The abnormal phonocardiographic findings are related to the elevation of left atrial pressure. When the left atrial pressure is elevated there is a delay in closure of the mitral valve which prolongs the time interval between the onset of ventricular depolarization and the mitral component of the first sound (Q-1 interval) (Fig. 5).

The opening snap occurs during the period of isometric relaxation when the left ventricular pressure falls below left atrial pressure. Elevation of left atrial pressure causes the mitral valve to open earlier and shortens the time interval between the aortic component of the second sound and the opening snap (2-O.S interval). As mitral stenosis becomes more severe, the left atrial pressure rises and the 2-O.S. interval becomes shorter (Fig. 5). Gorlin and Gorlin[3] demonstrated that when there was a large mitral valve area only a small increase in pulmonary capillary pressure was necessary to produce

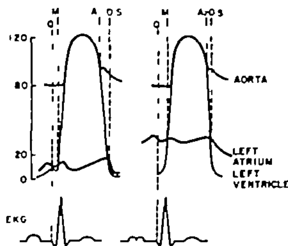


Fig. 5. The diagram on the left demonstrates the relationships of the Q-1 and 2-O.S intervals with normal left atrial pressure. The diagram on the right shows the prolongation of the Q-1 and the shortening of the 2-O.S intervals with elevation of the left atrial pressure.

increased flow. With progressively smaller valve areas, greater pressures were required to increase the flow.

The heart rate also influences the Q-1 and 2-O.S intervals. A short period of diastole is associated with a short 2-O.S interval. The effect of cycle length on these intervals has been investigated by several workers. Schillig[9] found that the decrease in the 2-O.S interval associated with increased heart rate was a function of the degree of stenosis of the mitral valve. This correlates with the clinical observation that patients with mitral stenosis do not tolerate tachycardia because a rapid rate results in an elevation of left atrial pressure. At very slow heart rates the area of the mitral valve ceases to be a significant determinant of the Q-1 and 2-O.S intervals because the left atrium can empty itself through a small valve if given enough time.[10] The 2-O.S. interval has greater predictive value when not corrected for heart rate provided that the rate is neither extremely slow nor extremely rapid.[11,12] Therefore, in the present study these intervals were not corrected for heart rate but the results of exercise tests were considered to be invalid if the heart rate 3 minutes after the completion of exercise was less than 60 per minute or greater than 100 per minute.

Systemic hypertension is another factor which influences the 2-O.S. interval. Bayer and associates[13] demonstrated prolongation of the 2-O.S. interval in systolic hypertension produced by norepinephrine. They also studied hypertensive and normotensive patients with mitral stenosis, and found that the 2-O.S. interval was shortened when the systolic blood pressure was below 110 mm. Hg and prolonged when systolic blood pressure exceeded 130 mm. Hg. The prolonged interval depended on the difference in pressure in the left ventricle between aortic valve closure and mitral valve opening, as well as the slope of the fall in pressure during the isometric relaxation of the ventricle.

Messer and associates[7] studied variations of the 2-O.S. interval occurring in patients with atrial fibrillation. They found that a short diastolic period was followed by a short 2-O.S. interval and that a long diastolic period prolonged the 2-O.S. interval. For this reason in this study, when patients were fibrillating, the 2-O.S. interval was measured in the cycle which followed a diastolic period that most closely approximated a heart rate of 75.

Heart failure and primary myocardial disease cause elevation of left ventricular early diastolic pressure and subsequently of left atrial pressure.[14] This shortens the 2-O.S. interval. It has been suggested that the 2-O.S. interval may also be influenced indirectly by the size of the left atrium, resiliency of the atrial wall, presence of thrombus or tumor in the left atrium, and the mobility of the mitral valve.[4] Mitral insufficiency and aortic insufficiency may also affect the 2-O.S. interval.

Mitral valvotomy has proved to be an excellent palliative operation for patients with mitral stenosis who are symptomatic. The selection of symptomatic patients for surgery is relatively easy when physical examination, electrocardiogram, chest x-ray film, and phonocardiogram show typical findings and there are no complicating valvular lesions. However, there are several groups of patients who are difficult to advise. These include patients whose symptoms seem to be out of proportion to the physical findings, mildly symptomatic patients in whom the physical findings are compatible with severe disease, postoperative patients whose symptoms are difficult to interpret, and patients whose physical activity has been so severely limited that symptomatology is difficult to evaluate. Although these patients represent a small proportion of the patients who are evaluated for surgery, they do represent a particularly difficult group. Brunner and associates[16] recently reported on 20 patients with severe mitral stenosis whose only complaint was slight dyspnea. Wood[13] pointed out the possibility of death from sudden intractable pulmonary edema in patients having severe mitral stenosis but minimal symptomatology. Harrison and Dexter[18] have shown the difficulties associated with the evaluation of patients after mitral valvotomy and have commented on the unreliability of many of the classic physical findings. They suggested that cardiac catheterization was frequently necessary for an accurate evaluation of these patients.

Wood[13] reported a recurrence rate in patients with mitral stenosis of 2 per cent per year or approximately 20 per cent in a 10-year period. Ellis[17] reported a reoperation rate greater than 20 per cent in 9 years. Although many of the patients with recurrent mitral stenosis will require a cardiac catheterization study, frequent cardiac catheterizations are not desirable and a simple, easily performed test for evaluating such patients would be helpful.

Most patients with mitral stenosis are asymptomatic at rest and develop symptoms only with mild to moderate exertion. When these patients are evaluated in the resting state, the true significance of the lesion may not be evident. Patients who appear to have lesions of equal severity when examined in the resting state may vary considerably in their response to exercise. For these reasons a standard exercise test has virtue as a simple screening procedure for evaluating patients with mitral stenosis. The alteration of the 2-O.S. interval with exercise is an easily measured parameter of the severity of mitral stenosis.

Summary

Eighteen of 20 patients with moderate and severe mitral stenosis had positive exercise phonocardiographic tests. None of the 10 patients with mild stenosis had a positive test. Four of 7 patients who had

positive tests preoperatively and were retested after mitral valvotomy had negative tests. The exercise phonocardiogram is a simple procedure for evaluating the severity of mitral stenosis.

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Mechanical performance of myocardium from hibernating and nonhibernating mammals

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It has long been recognized that one of the important obstacles to greater use of hypothermia in clinical medicine is the profound and sometimes catastrophic effect of low temperatures on cardiac function.

Thus, the physiology of hibernation has been of great interest to investigators, since hibernators are capable of withstanding body temperatures close to 0°C with no ill effects.

It is now well established that entrance into hibernation is an active process in the intact animal and may involve complex autonomic and endocrine mechanisms preceding as well as during the period of lowered body temperature. For instance, heart rate and probably metabolic rate decrease before body temperature begins to drop. Thyroid, adrenals, gonads, and other endocrine glands undergo marked changes during hibernation.[3] Thus, it is of considerable interest to consider to what degree these extracardiac effects determine the ability of the cardiovascular system of hibernators to function at very low temperatures.

It has been found that hearts of hibernating mammals and of poikilotherms function efficiently at very low temperatures both in vivo and in vitro, whereas those of nonhibernating species are severely compromised by temperatures below 20 to 25 C.[1-3] Hibernators in the nonhibernating or active state have been utilized in some studies; specimens actually in hibernation were used in a few. Direct comparisons of myocardial performance in hibernating and in active specimens of a single species are hard to find in the literature. It was thought that such direct comparison of tissues might provide interesting information about the physiologic determinants of the ability to hibernate.

Many comparative studies[4-illegible] which have been carried out have utilized spontaneously contracting preparations. In such studies, the effects of rate (which is profoundly affected by temperature) on contractility complicate the direct effects of temperature on mechanical performance. It was thought that a study was needed in which the rate of contraction was controlled, and for this reason isolated electrically driven myocardial strips were utilized. The effect of rate was then studied

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as a controlled variable by determining the force-frequency relationships at several temperatures

Methods

Five species were studied Hibernating species were represented by ground squirrels (*Citellus lateralis* and *C tereticaudus*) and the golden hamster (*Mesocricetus auratus*) Nonhibernators included the rat (Sprague-Dawley and Long Evans strains) and the guinea pig The normal body temperature for each of these species is 36-38°C

Ten to 15 animals of each of the five species were maintained in the animal quarters at an average temperature of 24°C Ten to 15 other animals of each species were placed in individual cages in a cold room maintained at 5-7°C Abundant wood shavings were available and an excess of standard laboratory food pellets were placed in the cages of all the animals, except the ground squirrels. Food was removed from the cages of the ground squirrels within 72 hours after they had been placed in the cold (this is thought to cause more prompt hibernation) All of the guinea pigs died within 72 hours. The rats survived for 7 to 14 days, but the number surviving 14 days was too small for useful study All of the hamsters survived 14 days and about 50 per cent survived several months. Of the survivors, only about 50 per cent hibernated (using as criteria a body temperature within 5 to 8°C of the environment and arousal from the dormant state in response to moderate handling stimulation) All of the ground squirrels hibernated within 1 week. Only 1 died probably because of an infection.

Isolated myocardial strips were prepared by decapitating or stunning and exsanguinating the animal and rapidly removing the heart to cold oxygenated solution containing NaCl 154 mM/L, KCl 5 6 mM/L CaCl$_2$ 5 0 mM/L NaHCO 7 1 mM L and dextrose 11 mM/L. Thin strips (one from each animal) were cut from the free wall of the right ventricle and were mounted in a temperature-controlled chamber[8] containing the solution described and gassed with 95 per cent oxygen and 5 per cent carbon dioxide. The preparations were equilibrated for 60 to 90 minutes with stimulation at 0.5 per second and temperature at 36° Isometric tension was measured with RCA 5734 transducer triodes and recorded on ink writing oscillographs. Stimuli were provided by Tektronix 161 pulse generators using supramaximal voltage at a pulse duration of 10 msec

The relationship of steady-state isometric tension to temperature was determined at the arbitrarily chosen rate of 0 5 stimuli per second After equilibration at 36 C the temperature was lowered at the rate of 1 per 2 to 3 minutes. Stimulus threshold voltage was repeatedly determined and the stimulus intensity was maintained at either approximately 1.5 times the threshold or 50 volts (the maximum available from the stimulator) whichever was less Recorded contractile tension was measured at 2° intervals from 36° down to the temperature at which no contractions could be elicited at the designated rate (at slower rates some preparations continued to respond to slightly lower temperatures) In order to permit statistical treatment the maximum contractile tension for each preparation was determined and set equal to 100 per cent All of the other measurements of tension were then converted to per cent of maximum

The force-frequency relationship was determined at three temperatures 35° 25 and 15°C Stimulus voltage was maintained as described in the preceding paragraph Stimulation was carried out successively at frequencies of 0 1 0.5 1 2,3 etc per second until the preparation failed to respond to each stimulus. Each frequency was maintained long enough for contractile tension to stabilize. The maximum contractile tension at each of the three temperatures was determined for each preparation and isometric tension at each other frequency was then expressed as per cent of this maximum

Results

Force temperature relationship In general the results obtained with the two nonhibernating species, and with the hibernators in the awake condition (Fig 1) supported the hypothesis that myocardial function would be more resistant to low

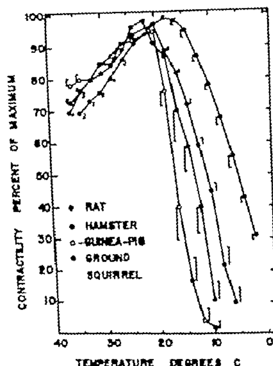


Fig. 1. Temperature-isometric force data for isolated right ventricular strips from nonhibernating species and hibernators in the awake state. Each curve represents the average of 4 to 10 preparations over the entire range of temperature. For each preparation the maximum contractility was set at 100 per cent and the measurements at every other temperature were related to it. Vertical bars indicate the standard error (S.E.).

temperatures in hibernators. However the apparent superiority of the myocardium of the rat to that of the hamster was unexpected. In order to rule out the possibility that the means computed using all of the data were biased by varying numbers of zero values (i.e. unresponsive muscles recorded as producing zero tension) the data for the lower temperatures were recalculated for each temperature using only data from the muscles still responding to stimulation with measurable contractions. However there was no change in the relative performance of the four types of myocardium.

It should also be noted that, in the temperature range of 36° to 27° all of the preparations showed an increase in contractile tension with decreasing temperature. This confirms the previous reports of many other authors[4] and suggests that above 20-22°C myocardial contractile force is not notably superior in hibernating species.

Fig. 2 contrasts the performance of myocardium from the hibernating species in the active and in the hibernating states. There were no significant differences between hibernating and nonhibernating ground squirrel myocardium and hibernating hamster tissue. However the contractility of nonhibernating hamster myocardial tissue fell to levels significantly lower ($p < .05$) than the levels of contractility of the other tissues at every temperature below 20°.

Another manifestation of the effect of temperature on myocardial performance is the temperature at which peak contractile tension is registered. Since it had already been found that the several species differed significantly in performance at low temperatures it was of interest to

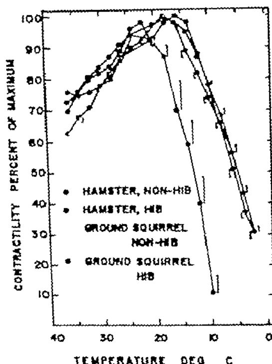


Fig. 2. Temperature-isometric force data for isolated right ventricular strips from hibernating species in both awake and hibernating conditions. See legend to Fig. 1.

Table I. Mean temperature at which peak isometric contractility was recorded for a contraction rate of 0.5 per second and arrest temperatures for this rate

Species	N	Peak contractility (Temperature ± S.E.)	P population	Arrest (Temperature ± S.E.)	P population
Guinea pig	10	20.8°C ± 0.42		13.4°C ± .79	a
Rat	12	21.5 ± 0.26	a,b	6.0 ± .54	b
Hamster nonhibernating	9	22.3 ± 0.44	b	10.2 ± .65	
Hamster hibernating	7	17.6 ± 0.20		<1.0†	d
Ground squirrel nonhibernating	6	16.5 ± 0.43	d	<1.0	d
Ground squirrel hibernating	4	15.5 ± 0.29	d	<1.0	d

Populations with different letter designations are statistically different $p < 0.05$
†Lowest temperature reached with apparatus used

establish the degree to which this was due to differences in peak temperature rather than differences in slope. A second temperature variable of interest was the temperature (arrest temperature) at which the isolated tissue no longer responded to maximal stimuli delivered at the standard rate (0.5 per second). Table I shows the results of these computations. By both measures, the ventricular tissue of the nonhibernating hamster was less tolerant of low temperatures than that of the nonhibernating ground squirrel and preparations from hibernating individuals of both species. The apparent superiority of rat myocardium to that of the nonhibernating hamster is again noted in the significantly lower arrest temperatures found for the rat.

Since it is well known that heart rate does not remain constant as body temperature changes, it was important to evaluate the influence of frequency of contraction on contractile performance at representative temperatures. The force-frequency curves obtained using animals in the nonhibernating state are shown in Fig. 3. The curves obtained for the "cold-resistant" species, rat and ground squirrel, were remarkably stable for the 20° temperature range studied. In comparison, the guinea pig and hamster preparations showed more marked reduction in high-frequency performance as temperature was lowered. This progressive reduction of the optimal frequency (contraction rate producing maximal contractility) and maximum follow frequency (highest stimulation frequency at which the muscle responds to every stimulus) has been previously reported by Kruta and Stejskalova.[4]

Changes in stimulus threshold. During determination of the force-temperature data, the temperature at which the stimulus threshold (as estimated from the stimulus voltage required) began to increase was noted. In all preparations, threshold remained approximately constant from 36 down to 20° or less and then began to rise steeply. The mean temperatures at which this steep rise began were: guinea pig, 17°; rat, 15°; hamster, 13°; and ground squirrel, 9°C. Data for the latter two species are for tissues from nonhibernating individuals.

Discussion

The data presented strongly support the hypothesis that certain intrinsic properties of the myocardium of hibernating species permit efficient function at low temperatures. However, these properties do not seem to be absent in all nonhibernating species, since we have shown that isolated rat myocardium is capable of responding to stimuli down to temperatures well below the lethal temperature (16 C.)[3] for the intact animal. Furthermore, since isolated myocardium was used in this study, it appears that integrated endocrine and/or central nervous system alterations are not required for effective cardiac function in all hibernators (a conclusion reached by Adolph).[11] Thus, low temperature per-

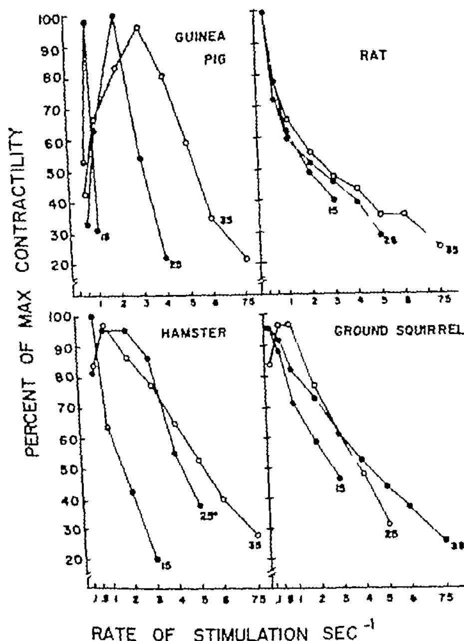


Fig. 3. Frequency-isometric force data determined for right ventricular strips from animals in the awake state. At 25° and 15° the maximum frequency plotted indicates the rate nearest the maximum follow frequency. Each curve represents the average of 4 to 10 preparations.

formance of myocardium from awake and active ground squirrels did not differ detectably from that of tissue from hibernating squirrels. In contrast, myocardium from hibernating hamsters was markedly more tolerant of cold than was tissue from active hamsters. This suggests that the biochemical milieu necessary for function at low temperatures is always present in ground squirrel heart but requires special adaptive changes in the case of the hamster. It is of interest that some authors[17] have been able to demonstrate significant changes in metabolism in hamster tissues during a period of exposure to cold preceding hibernation. These authors[17] and others[2,11]

have remarked upon the fact that the hamster enters hibernation much more slowly (usually several weeks) than do ground squirrels (a few days)

It is known that critical temperatures for survival of intact animals fairly closely approximate the arrest temperatures of spontaneously beating isolated myocardial preparations.[4] Thus, it is paradoxical that electrically driven rat myocardium should appear to have a tolerance of cold superior to that of the nonhibernating hamster since the heart in the intact hamster isolated spontaneously beating hamster heart and isolated hamster atria have all been shown to function at lower temperatures than do rat preparations.[4-6] However in none of the studies cited was contractility measured Furthermore since the measurements of contractility made in this study were relative the mechanical superiority of rat myocardium demonstrated in Fig 1 may be only relative and not absolute Since the force frequency relationship of hamster heart deteriorated more with decreasing temperature the lower arrest temperature (Table I) found for rats than for hamsters in this study may represent a manifestation of the greater temperature stability of the force frequency relation in rat heart (Fig 3) and the fact that the arrest temperature was determined using a fixed rate (0.5 per second) higher than the normal spontaneous rate for any species at these temperatures Adolph[11] has remarked that isolation of the heart affects its performance more in the hamster than in the rat or the mouse, and Lyman and Blinks[7] noted an inherent delicacy of the hamster heart and the fact that tissue cultures from infant hamster and rat heart were not detectably different in their response to decreased temperature

Finally it should be noted that the differences in mechanical performance of myocardial strips from the species studied were largely quantitative That is, increments in contractile force were observed in all preparations when the temperature was lowered from 36 to 22° and decrements were observed in all cases below 15 to 18°C. Nevertheless, the ability of hibernating hamster ventricle and both hibernating and nonhibernating ground squirrel ventricle to contract below 5°C sets these tissues apart from the others studied

Summary

The mechanical performance of electrically driven right ventricular myocardium from guinea pig rat hamster and ground squirrel was studied in vitro at temperatures from 1 to 36 C

Tissue from hibernating specimens (ground squirrels and hamsters) demonstrated significantly better performance (less diminution in isometric tension and lower arrest temperatures) at low temperature than did myocardium from nonhibernating species (guinea pig and rat) However myocardium from nonhibernating hamsters was demonstrably less tolerant of low temperatures than was tissue from hibernating specimens which suggests that a significant adaptation had taken place in individuals entering hibernation In contrast no significant difference between hibernating and nonhibernating ground squirrel myocardium was demonstrated

The myocardial force-frequency relationship was found to be quite sensitive to temperature in guinea pigs and hamsters but relatively resistant in rats and ground squirrels.

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Case reports

Traumatic rupture of a papillary muscle in a child

Case report and review of literature

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Rupture of a papillary muscle of the heart due to trauma to the chest is a rare lesion. The few cases reported have usually been associated with trauma of a severely violent nature and in adults. The purpose of this paper is to present one case of rupture of a papillary muscle in a child after nonpenetrating injury to the chest.

Case report

A 13-year-old white boy was admitted to Charleston Memorial Hospital on June 20, 1963, in a semicomatose condition. His 17-year-old sister reported that he had been well until the afternoon of June 18, 1963, when, while playing on a swing, he had fallen, hitting his chest on a stump. After the accident he was unconscious for some time. When he regained consciousness, he was short of breath and vomited twice.

Later that evening the patient was taken to a physician, and a laceration on the chin was sutured. The boy seemed to be well otherwise. On June 19, 1963, the patient vomited all day and was again taken to the family physician that evening, at which time he was dyspneic, had a rectal temperature of 102°F, and a heart rate of 160 beats per minute. He was given digitalis, morphine, and metaraminol, and was referred to the emergency room approximately 36 hours after the time of the accident.

Physical examination revealed a small, thin, acutely ill white boy with severe dyspnea. The blood pressure was 80/50 mm. Hg, heart rate 160, respirations 60, and rectal temperature 103°F. There was a sutured laceration in the midline of the chin and a large abrasion over the left upper anterior chest. The respiratory excursions were rapid, with some retraction of the intercostal spaces. There were moist inspiratory and expiratory wheezes throughout the lung fields. The heart sounds were obscured by the pulmonary noises; however, one of the examiners recorded a Grade 1 (6) systolic murmur at the apex. No thrill was felt. The patient was dehydrated, restless, confused, and disoriented.

The electrocardiogram (Fig. 1) revealed sinus tachycardia at a rate of 150, and a QRS axis of +150 degrees; there was clockwise rotation; the axis of the T waves was +75 degrees; R in Lead V; S-T segment depression in Leads III and aVF and elevation in Lead V, and Q waves in Lead I and aVL. The x-ray film of the chest disclosed the heart size in the upper limits of normal, bilateral pulmonary infiltrates consistent with pulmonary edema, and pleural effusion on the right. The white blood cell count was 29,700 with 86 per cent neutrophils, hemoglobin 15.5 Gm. per 100 ml., hematocrit 45 per cent. The corrected erythrocyte sedimentation rate was 15 mm. per hour. The sodium was 139 mEq., potassium 5 mEq., chloride 93 mEq., carbon dioxide 20 mEq. per liter. A throat culture grew Diplococcus and Klebsiella pneumonia organisms.

The patient was given oxygen, digitalis, and penicillin in intravenous infusion. His condition continued to deteriorate very rapidly, with severe dyspnea, tachycardia, elevated temperature, and cyanosis. About 5 hours after the patient had been admitted, pink frothy fluid began to appear from the mouth and nostrils. A tracheostomy was performed with suction of a massive amount of foam and pink fluid, and positive pressure breathing was applied.

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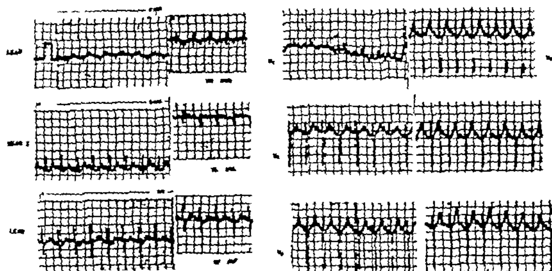


Fig. 1. Electrocardiogram.

The patient died in shock and acute pulmonary edema 9 hours after admission and approximately 45 hour after the accident.

Postmortem examination revealed that the posterior papillary muscle of the left ventricle had been torn across at its base from the underlying myocardium (Fig. 2). There was also a contusion on the lateral apical aspect of the left ventricle.

Discussion

The rupture of a papillary muscle of the heart has been the subject of several reviews.[1-4] Parmley, Manion and Mattingly[4] in a study of 546 autopsied cases of nonpenetrating injury to the heart, found 24 instances of rupture of a papillary muscle. In 23 of these cases there were other traumatic myocardial lesions, mainly myocardial rupture. Thus, the incidence of isolated papillary muscle rupture would be less than 2 in 1 000 cases of nonpenetrating traumatic injury to the heart. Traumatic rupture of a papillary muscle has been reported in only 6 cases. A brief description of those cases is as follows.

In 1920 Kleberger[5] reported the case of a soldier whose chest was contused by a grenade and in whom postmortem examination revealed rupture of the anterior and posterior papillary muscles of the right ventricle. Glendy and White reported the case of a 24-year-old seaman who thrown violently from a car and run over by a truck died 26 hours later with contusion

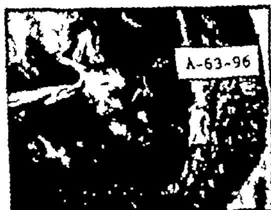


Fig. 2. The papillary muscle to the posterior cusp of the mitral valve is freely movable with extensive tearing from the underlying myocardium.

of the anterior surface of the left ventricle and rupture of the left anterior papillary muscle. The case of Payne and Hardy was that of a 51 year-old white man who was found unconscious beside a moving conveyor belt and who died 1 hour later with contusion of the anterior wall of the left ventricle and partial rupture of the left posterior papillary muscle. Cooley and associates refer to a case of ruptured papillary muscle of the anterior leaflet of the tricuspid valve after trauma. This case

reported in detail by Parmley and associates[4] was that of a 28-year-old man involved in an automobile accident in whom the diagnosis of tricuspid insufficiency due to traumatic rupture of a papillary muscle was made by right heart catheterization 4 months after the accident. The ruptured papillary muscle was repaired, but the patient died 12 hours postoperatively from massive hemorrhage from the right atrial appendage. The case reported by Osborn, Jones and Jahnke is that of a 33-year-old soldier with crushing injury to the chest and multiple injuries to the body which were sustained in an automobile accident in which the patient was thrown against the dashboard. Traumatic tricuspid insufficiency was diagnosed 3 months after the accident, and successful repair of the ruptured anterior papillary muscle of the tricuspid valve was accomplished. McLaughlin and associates[10] reported the case of a 19-year-old man thrown from a motorcycle onto the road after a collision with an automobile. A ruptured spleen and a ruptured kidney were removed, but the patient died 12 hours after the accident during induction of anesthesia for exploratory thoracotomy. At postmortem examination, rupture of the anterior papillary muscle of the left ventricle was found.

Myocardial infarction is the leading cause of nontraumatic rupture of a papillary muscle. In 1963 Maurice and Serousi[11] reviewed the world literature and listed 84 cases of spontaneous rupture of papillary muscle from all causes, 60 of which were due to myocardial infarction and 3 of which were due to nonpenetrating trauma to the thorax. Their report did not include cases reported by Parmley and associates, Cooley and associates, Arvay and Takacsy,[12] Drennan,[13] Borroni and Casadio,[14] Hendrich and Stoger,[15] Breneman and Drake,[16] and Hansen.[17] These and other cases[9,10,18-23] reported since raise the reported instances of rupture of a papillary muscle to 114. Six have been due to trauma.

Infection has been reported in 7 cases of rupture of a papillary muscle, and these are distributed as follows: syphilis, 2 cases (Merat[24] in 1803, and Spalding and Von Glahn[25]); vegetating valvulitis, 2 cases (Bertin[26] and Spanton[27]); myocardial abscess, 1 case (secondary to *Escherichia coli* septicemia, reported by Hackel and Kaufman[28]); bacterial endocarditis, 1 case (complicating ventricular septal defect, reported by Cooley and associates); embolic abscess to papillary muscle, 1 case (secondary to chronic pyelonephritis, reported by Hendrich and Stoger[15]). Periarteritis nodosa has been implicated in 1 case[5] in which myocardial infarction resulted from this condition involving the coronary arteries.

The clinical picture of rupture of a papillary muscle varies according to the side of the heart in which the lesion is located. The rupture of a papillary muscle in the left side is characterized by rapid onset of left heart failure, shock, acute pulmonary edema, and death. Failure on the left side is attributed to severe mitral insufficiency secondary to the anatomic disruption of the mitral valve. In the 3 reported cases of ruptured left ventricular papillary muscle due to trauma, death has occurred from 1 to 26 hours after the accident. The patient of the present report survived 45 hours after the trauma. One third of the patients in whom the rupture is a sequel to myocardial infarction die almost immediately after the rupture, and more than half die within the first 24 hours;[3] however, cases have been reported in which the patient survived for months. Breneman and Drake[16] reported 2 cases diagnosed during life in which death occurred 11 and 14 months after the presumed date of rupture. These two cases are the longest recorded instances of survival after papillary muscle rupture complicating myocardial infarction.

Rupture of a papillary muscle in the right ventricle causes less dramatic signs and symptoms than does rupture of a papillary muscle in the left ventricle. The signs and symptoms of tricuspid insufficiency subsequent to the rupture are slow in development. The clinical description and hemodynamic data of rupture of a right ventricular papillary muscle have been presented in the case reported by Parmley and associates[4] and in the case by Osborn and associates.[9] These 2 patients had dyspnea and fatigue on exertion 4 and 3 months, respectively, after the accident. In both cases the diagnosis of tricuspid insufficiency was made by right heart catheterization, and the ruptured papillary

muscle was successfully repaired. The difference in the clinical courses of traumatic mitral insufficiency and traumatic tricuspid insufficiency is attributable to the difference in pressures between the two ventricles.[9,21] The only instance so far reported of rupture of a tricuspid papillary muscle due to myocardial infarction is that of Eisenberg and Suyemoto.[31] This patient died 4 weeks after the occurrence of the rupture.

The differential diagnosis has been discussed by Craddock and Mahe,[8] Breneman and Drake,[19] and more recently by Holloway and associates.[28] Conditions to be considered in the differential diagnosis of rupture of a papillary muscle are rupture of the interventricular septum, rupture of an aortic cusp, rupture of the ventricle, rupture of the mitral chordae tendineae. In more than half of the cases of rupture of a papillary muscle a systolic murmur at the apex has been described. The absence of the murmur in some cases is attributed to the suddenness of death or to the wheezes and râles of pulmonary edema which obscure the cardiac sounds.

As in the great majority of cases of rupture of a papillary muscle the cause is myocardial infarction, the signs and symptoms preceding the rupture are those of recent myocardial infarction. However, those cases secondary to trauma are presented in a different setting. According to Kissane,[47] about 30 per cent of all patients with serious cardiac injuries come to the hospital unconscious and moribund. When consciousness is not lost, the most frequent complaints are weakness, dizziness, syncope, dyspnea, retrosternal pain, cough, palpitation, anginal syndrome, or disturbances in cardiac rhythm. According to the same author, more cases of traumatic heart disease are overlooked than diagnosed because the characteristic signs are not observed, because the patient is unconscious, or because the attention of the physician is distracted by severe injuries to other parts of the body. In our case, because of the patient's age and the findings of an apical systolic murmur, congestive heart failure, high temperature, leukocytosis, tachycardia, orthopnea, cyanosis, severe prostration, and weakness, the most important consideration was acute rheumatic carditis. Since pulmonary edema may be a manifestation of a pneumonic infection with a high degree of toxicity, an overwhelming pneumonia was also considered in this case.

Conclusion

The case is presented of a 13-year-old boy with rupture of the left posterior papillary muscle of the heart due to nonpenetrating trauma to the chest. This is the seventh case of rupture of a papillary muscle due to trauma, and, as far as we can determine, the only such case in a child reported in the literature.

The literature on this subject is reviewed and a total of 115 cases, including our case, of papillary muscle rupture from all causes is noted.

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Extensive accessory pulmonary arteries in the presence of relatively normal primary pulmonary arteries

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Anomalies of arterial vessels to the lungs are of three general types: absence of pulmonary arteries,[1-3] pulmonary arteries originating anomalously,[illegible] and anomalies of the bronchial arteries and other systemic collateral vessels to the lung. This last group includes bronchial arteries with compensatory hypertrophy, as in patients with pulmonary atresia,[1-3] and "accessory pulmonary arteries."[illegible] Accessory pulmonary arteries refer to a disproportionate development of the bronchial arterial system beyond that which could be anticipated on the basis of development of the true pulmonary arteries. Also called "aberrant" by a previous author, these arteries have been described in many vertebrates, ranging from amphibians and reptiles to mammals and man.[illegible] In 1837 Hyrtl[10] described accessory pulmonary arteries as a normal occurrence in snakes. McCotter[11] in 1910 reviewed the literature to 1777 and found 4 cases in which accessory pulmonary arteries supplied normal lungs. In 5 other cases the lungs were found to be abnormal. In a more recent review, Findlay and Maier[4] found 67 cases of anomalous systemic vessels. A 75 per cent incidence of significant associated anomalies of the heart or great vessels was found in the cases of suprahilar arteries to the lung. Cole,[illegible] therefore, believed that these vessels were compensatory to decreased pulmonary blood flow. In cases demonstrating abnormal systemic vessels to the lung arising below the pulmonary hilum, concomitant abnormalities of the heart or great vessels were observed in only 16 per cent of the cases; however, lung anomalies were found in 70 per cent of these.

Cases of dual pulmonary blood supply have been reported before, but no topographical details or illustrations of the accessory vessels were provided in most reports. Therefore, we thought that it would be worth while to present the case of our patient in whom four impressive accessory pulmonary arteries were demonstrated during life.

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Case history

The patient, a 6-year-old white girl, was referred to the University Hospital for evaluation of congenital heart disease that was first suspected at the age of 6 months because of a heart murmur. History revealed an episode of perioral cyanosis at the age of 9 months. At 2 years of age very mild cyanosis of the lips and nail bed had become evident. Cardiac status was evaluated at the age of 3 and a diagnosis of tetralogy of Fallot with patent ductus arteriosus was suspected. The child had been otherwise entirely well participating without difficulties in ordinary activities. Except for poor gain in weight there were no complaints.

Physical examination revealed a small child questionably cyanotic with abnormalities confined to the heart. There was an active precordium, with the cardiac impulse both at the apex and along the lower left sternal border. A systolic thrill along the lower left sternal border could be palpated. The

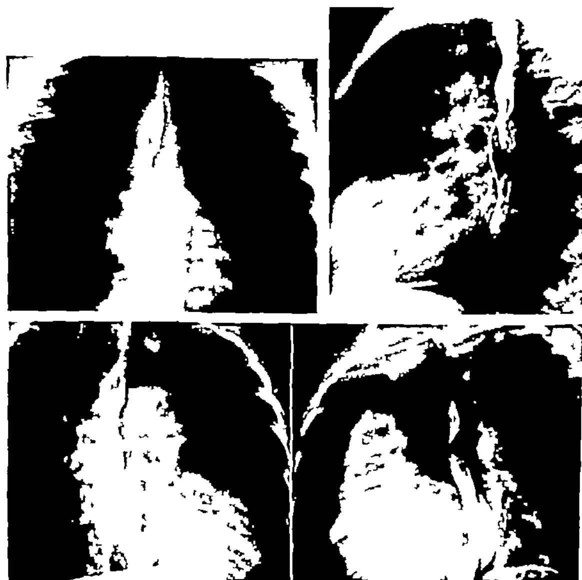


Fig. 1. Radiographs of the heart with barium swallow. *Upper left*, Postero-anterior view. *Upper right*, Lateral view. *Lower left*, Right anterior oblique view. *Lower right*, Left anterior oblique view. The heart is moderately enlarged and there is a wide supracardiac density suggesting a prominent ascending aorta. Note the impression on the esophagus at a level slightly below the aortic arch, suggesting an anomalous vessel. The pulmonary artery is not prominent and the peripheral vascularity is somewhat diminished. The pulmonary veins and left atrium are possibly slightly enlarged.

second heart sound was single and soft at the second left intercostal space, where a Grade 3/6, blowing crescendo-decrescendo, machinery type of murmur was heard. An electrocardiogram revealed a vertical axis, and a deeper S in Lead V_1 than normal but the tracing was otherwise within normal limits. X-ray films of the heart with barium swallow revealed a moderately enlarged heart, with a very prominent ascending aorta (Fig. 1). An impression on the esophagus at a level slightly below the arch of the aorta suggested an anomalous vessel. The pulmonary arteries were not prominent, and the pulmonary vascularity was perhaps diminished. Cardiac catheterization and an angiocardiogram from the right ventricle revealed, basically, a tetralogy of Fallot with an arterial oxygen saturation of 87 per cent (Fig. 2). A pressure gradient of 59 mm. Hg was recorded at the infundibular level; an additional gradient of 37 mm. Hg was present at the pulmonary valve. The pulmonary arterial pressure was 12/5 mm. Hg. There was a step-up in oxygen saturation of 10 per cent at the level of the pulmonary artery. A biplane angiocardiogram recorded from the aortic root revealed additional findings of three large bronchial arteries and an additional artery to the lungs from the right subclavian artery (Figs. 3, 4, and 5). The first of these anomalous arteries was shown to arise from the superior portion of the aortic arch, at the level of the left carotid artery; after arching upward over the aortic arch, it descended posteriorly out into the right lung field. This artery appeared to be quite tortuous and stenosed in some areas. The second and third bronchial arteries arose from the descending portion of the thoracic aorta and went to the left lung field. The fourth anomalous vessel originated from the subclavian artery on the right side and descended into the right lung field. Although there were connections between accessory and primary pulmonary arteries of sufficient size to produce a sizable increase in oxygen saturation and opacification with contrast material, the pressure in the pulmonary artery was not elevated. In view of the patient's good physical condition and a blood hematocrit of only 45 per cent, surgical correction of this complex lesion seemed to be unwarranted at the present time.



Fig. Right ventricular angiocardiogram, depicting a small main pulmonary artery and right and left pulmonary artery branches. Note also the filling of the dilated ascending aorta via ventricular septal defect.

Discussion

Accessory pulmonary arteries have been regarded as anatomic curiosities, and the main interest in them has centered about their possible embryologic significance which remains obscure. However, with the development of modern thoracic surgery and the advent of open heart surgery, such anomalies take on a new significance. The thoracic surgeon is likely to find infrahilar anomalous pulmonary vessels during operation for pulmonary parenchymal and diaphragmatic lesions.[9] He may encounter suprahilar anomalous pulmonary vessels when he attempts correction of a cardiovascular anomaly.[10] It is only when their presence is recognized that serious surgical complications can be avoided. Harris,[9] in 1940, stressed this point by presenting the case of a 5 year old child who died during lobectomy when an anomalous pulmonary artery arising from the descending aorta and entering the posterior segment of the lower left lobe was inadvertently cut. A similar danger exists during open heart surgery in the presence of an unrecognized dual vascular supply to the lung and anastomotic connections between the two vascular systems. The drainage is usually through the pulmonary veins, and the quantity of return to the left side of the heart during cardiopulmonary bypass may be quite large. In addition, these arterials have often been found to be fragile and tortuous and sometimes surrounded by adhesions.[6]

A dual supply of blood to the lungs has been associated with widely different clinical pictures. Some cases are clinically latent and are discovered accidently. Cioni's case (reported by Findlay) is an interesting one—demonstrating dual circulation to the right upper lobe of the lung from both the greater and lesser circuits for 60 years without apparent damaging

Recurrent ventricular tachycardia associated with complete heart block

Observations in a patient with the simultaneous use of a single-stimulus implanted myocardial pacemaker and a "coupled-pulse generator"

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Recurrent ventricular tachyarrhythmia is one of the most frequent mechanisms underlying Adams-Stokes attacks[1-3] and is commonly associated with some degree of abnormal A-V conduction. Electrical stimulation of the heart is the therapeutic method of choice in the prevention and treatment of recurrent episodes of ventricular tachycardia in the presence of an underlying A-V block.[1-3] Recently Lopez and associates[4] described two methods to reduce the frequency of effective ventricular contractions using pairs of electrical stimuli properly spaced, delivered by an artificial pacemaker. Chardack and associates, in dog experiments and in some clinical cases, have shown the successful use of paired-pulse pacemaking in slowing the heart rate in supraventricular and ventricular tachycardias. Braunwald,[6,7] Ross,[8] and Cranefield[10] and their associates reported a marked augmentation of the contractile response of the ventricle with the paired stimulation and slowing of the heart rate. An attempt to apply this new technique in a patient with recurrent bouts of ventricular tachycardia associated with Stokes-Adams episodes secondary to a postoperative complete heart block, is reported.

Case report

A 49-year-old housewife was readmitted for the third time to the Henry Ford Hospital on Feb. 2, 1965, with a 5-year history of progressive symptoms of congestive heart failure characterized by exertional dyspnea on one flight of stairs, four-pillow orthopnea, inability to do her housework, ankle edema, and marked fullness and distention of the upper abdomen which was partially relieved by diuretic injections. The patient had a known history of rheumatic heart disease, and during her first admission in 1960 a transthoracic left heart catheterization revealed minimal mitral stenosis with a 3 mm Hg gradient and associated mild mitral insufficiency by the Evans-blue dye technique. The patient was advised to follow a conservative program with salt restriction, diuretics, and digitalis. In December 1964 she was hospitalized with the previously described symptoms of congestive heart failure.

Physical examination revealed a well-developed woman who was in no acute distress. The blood pressure was 120/80 mm Hg. The apical rate was 104 per minute with atrial fibrillation. The temperature was 98.6°F. The neck veins were slightly distended

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at 45 degrees. The apex impulse was palpable in the fifth intercostal space 11 cm from the midsternal line. There was a slow sternal lift. On auscultation, the apical first sound was well preserved and was followed by a Grade 3/6 holosystolic murmur that radiated to the left axilla. There was an opening snap followed by a Grade 2/6 early diastolic rumble that was best heard medial to the apex. There was a Grade 3/6 holosystolic murmur over the tricuspid area which became accentuated on deep inspiration. The second pulmonic sound was increased. The lungs were clear to percussion and auscultation. The liver was easily palpable 4 cm at the midclavicular line and 8 cm at the midline with systolic expansions. There was pitting edema of both legs.

Laboratory data. The hemoglobin was 13.2 Gm per 100 ml, the leukocyte count was 5,600 per cubic millimeter with a normal differential. Serum creatinine, electrolytes, and urinalysis were normal. The electrocardiogram revealed atrial fibrillation and digitalis effect. The chest fluoroscopy showed marked cardiomegaly. The transverse diameter measured 170 mm as compared to 135 mm on the previous study performed in 1960. The left atrium was very prominent and there was also enlargement of the right atrium (see Fig. 1). No intracardiac calcification was observed. A right heart catheterization performed on Feb. 3, 1965, revealed slight elevation of the mean pulmonary wedge and right ventricular pressures (see Table I). There was evidence of insufficiency of the tricuspid valve as suggested by the prominent V waves in the atrial and superior vena cava recording (see Fig. 2).

The clinical impression was that of rheumatic heart disease with minimal mitral stenosis and insufficiency associated with tricuspid insufficiency. In view of the progression of her symptoms and the increasing cardiomegaly, a surgical consultation was obtained and the patient underwent open-heart surgery on March 4, 1965. At operation, exploration of the mitral valve revealed minimal insufficiency without significant stenosis. The tricuspid valve was found to be widely dilated and grossly incompetent. In view of the marked dilatation of the annulus and small size of the tricuspid valve leaflets, the surgeon elected to replace the tricuspid valve with a large Starr-Edwards prosthesis.

In the immediate postoperative period the patient recovered uneventfully and was transferred to the Special Care Unit with stable vital signs and good urinary output. The electrolytes, creatinine, and serum bilirubin remained within normal limits during the entire postoperative period.



Fig. 1. Chest roentgenogram showing the increased transverse diameter of the heart and marked prominence of the right atrium.

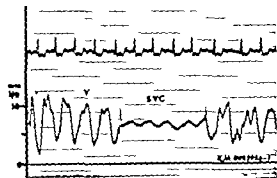


Fig. 2. Superior vena cava pressure pulse showing prominent V waves.

As shown in the serial electrocardiograms (Fig. 3,B, C, C', C'') a complete A-V block was recorded on the first postoperative day with a subsidiary A-V junctional rhythm at a regular rate of 60 per minute, and short runs of ventricular tachycardia were also observed (Fig. 3,C, C', C''). From the second to the seventh postoperative days, no antiarrhythmic drugs or digitalis were given to the patient. She continued to improve satisfactorily with the exception of the persistent A-V block. On the sixth postoperative day (Fig. 3,E, E') the A-V block was still present, atrial fibrillation had replaced the sinus P waves, and some premature ventricular contractions were noted. On March 11, 1965, the patient began to have more frequent ventricular ectopic beats in bigeminal fashion, and procainamide hydrochloride was started, 250 mg. every 4 hours for a total of six doses orally. The following day the ventricular premature contractions persisted, and at 5:00 P.M. the patient experienced an episode of Stokes-Adams syncope, most

Table I. Cardiac catheterization data

Site	Pressures (mm. Hg)		Oxygen (vol. %)	Saturation (%)
	Systolic/Diastolic	Mean		
Superior vena cava		6		
Right atrium		7		
Right ventricle	32/0–6			
Main pulmonary artery	30/12			
Right main pulmonary artery	32/13	18	11.5	65
Left pulmonary wedge		14		
Right pulmonary wedge		13	17.3	98
Femoral artery			17.2	97

Oxygen consumption 218.9 ml./min.
Oxygen capacity 17.7 vol. per cent
Cardiac output 3.84 L./min.
Cardiac index 2.4 L./min./M²

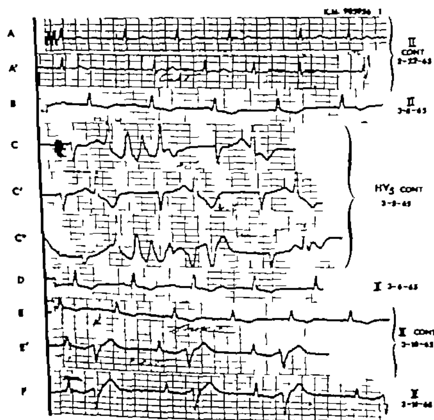


Fig. 3. A and A'. Continuous Lead II taken before operation. B, C, C', and C''. Leads II and V5, respectively, taken on the first postoperative day showing complete A-V block and repetitive paroxysmal ventricular tachycardia. D. The complete A-V block persists. E and F. Show atrial fibrillation with persistent complete A-V dissociation and frequent ventricular premature beats with a fixed coupling.

likely secondary to a bout of ventricular tachyarrhythmia from which she recovered in less than 2 minutes after external cardiac massage and mouth to-mouth beathing During the following 24 hours, frequent ectopic ventricular contractions were again noted and a second Stokes-Adams episode occurred which was controlled rapidly with a single external D C countershock

In the presence of a postoperative complete A V block which persisted for more than 7 days and was complicated by recurrent episodes of ventricular tachycardia with Stokes-Adams seizures, the indication for artificial electrical pacing of the heart seemed to be mandatory In this particular case the simpler intravenous pacemaking technique was not feasible because of the presence of the Starr Edwards prosthesis in the tricuspid area A Chardack-Greatbach pacemaker unit was then implanted and two additional electrode wires were inserted in the left ventricle for possible use with the paired pulse generator A tracheostomy was also performed for assisted respiration

After the implantation of the artificial pacemaker at a fixed rate of 74 per minute the frequent premature ventricular contractions persisted and during the subsequent 5 hours the patient had four more episodes of ventricular tachyarrhythmia which required repeated external counter shocks The slow intravenous administration of procainamide failed to decrease the ventricular ectopic activity In view of the failure of the single pacemaker stimulus to control the recurrent ventricular tachycardia the paired pulse generator was connected to the two additional electrode wires previously inserted in the left ventricle.

As can be seen in Fig 4,*A* the two stimuli of the coupled pacemaker at a rate of 80 per minute predominate in their competition to capture the ventricular depolarization as compared to the smaller single stimulus at a slower fixed rate of 74 per minute. This represents an interesting example of atrial fibrillation with complete atrioventricular block and two different simultaneous electronic parasystolic foci competing for the control of the ventricles In addition in the same illustration several premature ventricular beats can be observed representing a very active ventricular ectopic focus. At its original setting (interval 170 msec rate 80 per minute width 3 msec and amplitude 9 milliamperes) the paired pacemaker was giving rise to a single ventricular depolarization for each pair of electrical stimuli (Fig 4,*A* seventh pair) The single smaller electrical artefact stimulus can be followed easily in Fig 4,*A* capturing the first ventricular depolarization before the arrival of the first paired stimuli and then because of its slower rate (74 per minute) it can be seen superimposed on the second paired stimuli giving rise to a different QRS configuration (Fig 4,*A* second electronically induced beat) which probably represents a fusion beat It then proceeds to "drift" behind the paired stimuli until stimulus number 8 (*Fig 4,A*) *falling* after the refractory period of the preceding ventricular complex, captures the ventricular depolarization and continues to do so for seven successive impulses The first two of these captures by the single pacemaker represents an example of paired pacing when considered in relation to the preceding depolarization created by the paired pacemaker unit It also clearly demonstrates that our initial setting for the time interval of the paired stimuli (170 msec.) was relatively too short to induce the more appropriate paired electrical depolarization of the ventricles

In order to demonstrate graphically the inability of the single artificial pacemaker to control the ventricular arrhythmia the coupled generator was turned off as shown by the arrow in Fig 4,*B* After a transient control of the rhythm by the single-stimulus pacemaker alternating with frequent ventricular premature beats, by the end of strip *E* and at the beginning of strip *F* the reappearance of short runs of ventricular tachycardia became obvious. The "paired generator was quickly restarted (see arrow in Fig 4 *F*) with subsequent inhibition of the ventricular tachyarrhythmia and resumption of the initial competitive action between the two electronic pacemakers as previously discussed

Designed and manufactured by Medtronic Inc Minneapolis Minn

Fig. 4 Continuous Lead II with short interruption (from *D* to *E*), recorded at a paper speed of 50 mm/sec except for that part of the tracing enclosed between the arrows of strips *E* and *F* when it was changed to 25 mm/sec. *A* shown in Fig. 4. Tall paired stimuli artefacts (↑↑) at a rate of 80/min in competition with a smaller single-stimulus electronic artefact (↓) at a rate of 74/min. *B* The arrow indicates the instant when the coupled pacemaker generator was 'turned off' and the single-stimulus pacemaker controls the ventricular rhythm with frequent premature ventricular beats present. *C* and *D* Frequent ventricular ectopic beats persist with a fixed coupling. *E* A short run of ventricular tachycardia recorded. *F* Short runs of ventricular tachyarrhythmia persist. The arrow indicates the instant of re-activation of the coupled-pulse generator and simultaneous change of paper speed to the initial 50 mm/sec. *G* Similar to *A* with occasional premature ventricular beats preceding the [illegible] artefacts (fifth, sixth and seventh paired stimuli).

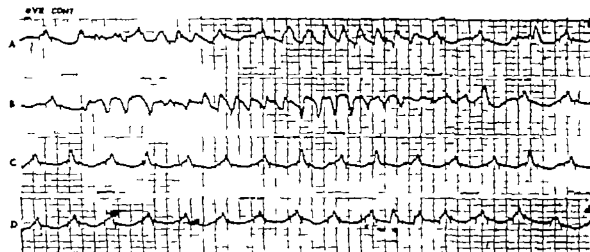


Fig. 5. Induced stimuli artefacts of the coupled-pulse generator at different settings. *A*, Interval of 150 msec., rate 84/min., amplitude 3.5 milliamperes, and width 3 msec., showing short runs of ventricular tachycardia. *B*, Interval 170 msec., rate 84/min., amplitude and width unchanged, again showing recurrent ventricular tachycardia. *C*, Interval 150 msec., rate increased to 95/min., other values unchanged, showing a more regular rhythm with occasional taller QRS complexes which might represent fusion beats or aberrant conduction (second, fourth, eighth, tenth, and fourteenth complexes). *D*, Interval 150 msec., the rate of the paired pacemaker was increased to 100/min., with only one premature ectopic beat recorded in this strip (eleventh).

The simultaneous use of the two pacemaker units definitely helped to control the recurrent bouts of ventricular tachycardia during the 12 hours of their combined action (Fig. 4*G*), maintaining an adequate blood pressure. We were concerned, however, by the fact that, as a result of the competitive action between the two pacemakers, the average apical rate was rather high (from 110 to 120 per minute) and, as shown in Fig. 4*G*, the ectopic ventricular focus was still active (the QRS complexes preceding the fifth, seventh, and eighth paired stimuli). The decision was then made to attempt to control the patient's rhythm at a more stable rate using only the paired pulse generator stimuli. The Chardack unit was turned off with the use of the Keith needle.

As shown in *A* and *B* of Fig. 5, the paired pacemaker, at that particular setting, was unable to control the recurrence of short runs of ventricular tachycardia. An attempt was made to overcome the ectopic ventricular focus by gradually increasing the rate of the paired stimuli without changing the time interval. As recorded in Fig. 5,*D*, when the rate was increased to 100 per minute, it was possible to obtain a more regular rhythm with a more definite suppression of the ectopic ventricular focus. During the slower rate (Fig. 5*C*), we can observe intermittent taller QRS complexes (second, fourth, eighth, tenth, and fourteenth) which most likely represent fusion beats between the ectopic ventricular focus and the first stimulus of the paired pacemaker. In Fig. 5*D* only one ectopic beat (number 11) was recorded, indicating a better inhibition of the ectopic focus.

At this time, the blood pressure remained stable at 110/70 mm. Hg and the urinary output, which averaged 20 c.c. per hour during the preceding 12 hours, increased to 50 c.c. per hour. Unfortunately, 4 hours later the patient developed another episode of syncope that required a single defibrillation countershock, followed by another more severe episode 3 hours later from which the patient did not recover in spite of external massage, countershock, assisted respiration, and a diversity of cardiac stimulants. No electrocardiogram was obtained during the terminal event, but according to the attending resident physician the cardioscope showed evidence of ventricular tachyarrhythmia followed

by ventricular fibrillation more clearly visualized after the paired unit was disconnected.

Permission for autopsy was limited to examination of the chest and at post mortem examination the lungs showed only congestion. The heart weighed 510 grams there were numerous pericardial adhesions. The left atrium was moderately dilated. The mitral valve was stenotic having a fish mouth appearance when viewed from the atrial aspect. The commissurotomy clefts were well visualized. The mitral ring measured 7.5 cm in circumference. The leaflets were thickened the attached chordae tendineae were thickened fused and shortened. There was slight dilatation and hypertrophy of both ventricles the left measured 1.3 cm and the right measured 0.5 cm in thickness. The myocardium was reddish brown and firm without apparent scarring. The Starr Edwards prosthesis was in good position and the suture line appeared to be intact. The right atrium appeared to be moderately dilated. The pulmonic and aortic valves were normal the ventricular and atrial septa were intact and the endocardium was smooth. The coronary arteries were widely patent showing minimal arteriosclerotic changes. Radiographic examination after injection with radiopaque material confirmed their patency throughout.



Fig. 6. Photomicrograph demonstrating involvement of the A V node by the healing process after replacement of the tricuspid valve. A fibrin deposit (*F*) divides the atrioventricular node (*A V*) in its central portion. Hematoxylin and eosin ×33



Fig. 7. Magnification of Fig. 6. The healing response to surgical trauma and the fibrin plug (*F*) in the A V node are well shown. Hematoxylin and eosin ×115

Microscopic examination revealed fibrous thickening of the mitral valve and of the surgically resected tricuspid leaflets and hypertrophy of myocardial fibers. Occasional small areas of perivascular fibrosis were present, but no evidence of active rheumatic disease was found.

Subserial sections were taken through the musculature of the conduction system. Traumatic pericarditis was present overlying the sinus node, and a few sutures and hemorrhagic foci were seen in its vicinity. The node showed fibrosis and fatty infiltration disproportionate to the age of the patient.[13] The bundle of His and its branches appeared histologically to be normal, but the atrioventricular node and the immediately surrounding area were involved by a florid fibroblastic proliferation and round cell infiltrate that extended from the base of the septal leaflet of the tricuspid valve, indicative of tissue repair at the site of surgical injury. In addition, a deposit of fibrin extended completely across the central part of the node (Figs. 6 and 7). This was interpreted as the result of the passage of a suture through this area, injuring the node and producing complete heart block.

Discussion

Electrical stimulation of the ventricles is the therapeutic method of choice[1,2] in the prevention of Stokes-Adams episodes caused by bouts of ventricular tachyarrhythmia in association with a complete atrioventricular block. The use of digitalis and antiarrhythmic drugs is generally considered to be contraindicated. In the case reported, with postoperative heart block, the replacement of the tricuspid valve by a Starr-Edwards prosthesis made the use of the simpler intravenous pacemaker technique impossible, and the implantation of a myocardial pacemaker was carried out. Two additional electrode wires were implanted in the left ventricle in order to make possible the use of the "coupled pulse generator" in the control of the rapid ventricular tachycardia. In this patient it was clearly demonstrated (see Fig. 4) that the single-stimulus pacemaker at a fixed rate of 74 per minute failed to control the arrhythmia.

The "coupled pulse generator" was then connected and after the single pacemaker unit was turned off, we found that by increasing the rate of the "paired unit" to 100 per minute, the ectopic ventricular focus remained inhibited for a longer period of time but unfortunately the results were transient and a fatal outcome could not be prevented. As can be observed in the preceding tracings (Figs. 4 and 5), at no time during the use of the "paired pulse generator" were we able to obtain the second additional premature ventricular depolarization without mechanical response as is required for a true "paired pacemaking stimulation." Only by a more precise adjustment of the time interval between the two stimuli of each pair will it be possible to obtain the desired paired pacemaking.

Although some authors[4] were able to slow both the rate of electrical depolarization and the mechanical rate with a single ventricular depolarization for each pair of stimuli, other authors found in dog experiments, that attempts to slow the heart electrically without producing two depolarizations for each contraction were largely unsuccessful and when they were consistently successful only minimal slowing could be obtained.

We could speculate that in this case, if we had proceeded to increase the rate of the single-stimulus pacemaker or of the "coupled-generator" to 110 or even 120 per minute, as was approximately maintained by the competitive action of the two different electronic pacemakers, the fatal arrhythmia could probably have been prevented. On the other hand, a more correct use of the paired pulse generator could have been a better solution to the problem. Another remote possibility was that of ventricular fibrillation triggered by the stimuli of the artificial pacemaker, as recently reported.[11]

Summary

Recurrent bouts of ventricular tachyarrhythmia with Stokes-Adams episodes, in the presence of a postoperative complete heart block, represents a therapeutic challenge. This is compounded when the tricuspid valve has been replaced by a Starr-Edwards prosthesis. An attempt to control the ventricular tachycardia with an

implanted myocardial pacemaker at a fixed rate of 74 per minute failed to abolish the arrhythmia. Temporary control of the ventricular ectopic focus with the additional use of the coupled pulse generator was recorded.

Some of the difficulties encountered in the clinical use of the new technique of paired stimulation and the hazard of complete heart block in tricuspid valve replacement should be emphasized.

Addendum

Since this paper was submitted for publication an important series of articles on paired pulse stimulation and post extrasystolic potentiation in the heart has been published.[14]

We wish to express our appreciation to Dr. A. R. Morales for the pathology report, including a careful study of the conduction system, and to Miss V. Chubran for typing the manuscript.

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Clinical pathologic conference

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Clinical summary

The patient was admitted to our institution at the age of 5 days because of marked generalized cyanosis and intermittent episodes of tachypnea. The clinical impression of hypoplastic right heart with tricuspid atresia and pulmonary flow originating from a patent ductus arteriosus defect was supported by the angiocardiogram. During the next 2 days the infant developed increasing respiratory distress and cyanosis, and surgery was decided upon. At operation the external appearance of the heart was that seen in tricuspid atresia with a large right atrium, a rudimentary right ventricle, and a small pulmonary artery arising from this chamber. An attempt was made to pass a dilator from the right ventricle through the pulmonary valve. However, no tract could be located. A temporary clamping of the proximal main pulmonary artery had no effect upon the cardiac action. After due consideration the pulmonary artery was amputated just distal to the pulmonary valve and the atretic valve could be visualized. An end-to-side anastomosis between the pulmonary artery and the ascending aorta was constructed and carefully tailored to measure about 3 mm. in diameter. The extremely cyanotic heart and surrounding tissues immediately improved and oxygenation appeared to be satisfactory. The postoperative clinical findings indicated satisfactory palliation.

The infant was discharged on the fourteenth postoperative day only to be readmitted 5 days later in severe respiratory distress with the clinical findings of bronchiolitis. The radiographic findings were those of atelectasis and probable pneumonia of the right upper lobe. The continuous murmur indicated patency of the surgical anastomosis although the x-ray film showed persistence of decreased pulmonary vascular markings. Gradual clinical improvement ensued without total clearance of the atelectasis of the right upper lobe in spite of bronchoscopic aspiration. Within the next 3 months the infant was admitted for the third and fourth times for periods of 3 weeks and $5\frac{1}{2}$ weeks respectively. Each admission was prompted by severe respiratory distress due to pulmonary infection and obstruction with signs of marked hypoxia. A lobectomy was performed during the fourth hospitalization because of persistent atelectasis. Examination of the surgical specimen showed atelectasis and chronic bronchitis. No microorganisms were demonstrated.

These four hospitalizations were dominated by periodic and profound episodes of hypoxia, initially because of markedly decreased pulmonary flow and subsequently secondary to a combination of inadequate pulmonary perfusion and ventilation. Liberal antibiotic therapy was employed in addition to the physical measures of humidification and aspiration.

During the next 2 years the infant progressed reasonably well. Both growth and development showed slow but steady advance. She remained moderately cyanotic. X-ray examination revealed a slowly increasing heart size and hypoperfusion of the lung. Serial electrocardiographic tracings showed a further increase in the degree of left ventricular hypertrophy as well as the gradual emergence of a pattern of right atrial hypertrophy. Therefore plans were made to readmit the patient for further surgical consideration including the enlargement of the interatrial communication. However, before this plan could be carried out, she was brought to our hospital in a semicomatose state for her fifth and final admission. On the morning of hospitalization the patient developed rapid labored respirations followed by unconsciousness which persisted until her admission 4 hours later. No known precipitant such as trauma, aspiration of a foreign body, or ingestion of toxic substances, could be established, and the infant had appeared to be well upon arising. No convulsive disorder was known to exist nor was there a history of diabetes. She received oxygen while being transported to another hospital, where morphine was given before she was referred to our service.

On admission the infant was afebrile with

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heart rate of 168 per minute and a blood pressure of 94/64 mm. Hg. She showed bouts of extreme irritability with a shrill, high-pitched cry. The cyanosis was of moderate severity and she was adequately hydrated. Bilateral hyperactive deep tendon reflexes with ankle clonus and Babinski signs were present. The neck was supple and the Kernig and Brudzinski signs were negative. Forced grasp and suck reflexes were found. No murmur could be heard with certainty because of respiratory effort. The murmur was heard later but appeared to be less intense than in the immediate postoperative period. Urinalysis was negative. The blood count showed a hemoglobin of 15.3 Gm. per cent, hematocrit, 48 per cent, WBC, 20,250 with a differential of 54 per cent polymorphonuclears, 30 per cent bands, 12 per cent lymphocytes and 3 per cent monocytes. Examination of the venous blood revealed Na, 143 mEq./L., K, 5.9 mEq./L., Cl, 113 mEq./L., CO_2, 12.3 mEq./L., Ca, 10 mg per cent, pH 7.26, pCO_2, 22.0 mm. Hg and base excess −15.8 mEq./L. Viral serum titers were less than 1:8 for EEE, WEE, St. LE, Polio 1,2,3, Cox A&B, Echo 6&9 and Herpes. A skull x-ray film was within normal limits. The electroencephalogram showed changes compatible with diffuse encephalopathy. A lumbar puncture revealed clear colorless fluid under an opening pressure of 270 mm. The protein measured 17 mg per cent, sugar 110 mg per cent, and chloride 130 mEq./L. There were no cells, and bacteriologic cultures were sterile.

After the patient had been hospitalized her temperature rose to 104°F (rectal) and she was placed on hypothermia at 92°F (rectal) for the first 2 weeks of her hospital course. In this period she was given high doses of penicillin and streptomycin. The patient developed decerebrate posture and seizures which did not respond to anticonvulsant therapy. Intravenous sodium bicarbonate was employed in an attempt to correct the acidosis. Her clinical state remained unchanged. After the discontinuance of hypothermia her temperature rose to 100°F (rectal). On the ninth hospital day feeding by nasogastric tube was begun, and the next day the patient developed a severe diarrhea. Pseudomonas was recovered from the stools and now 2 weeks after admission. *Candida albicans* was also obtained from the nasal culture at this time. On the twenty-third hospital day a blood culture yielded Pseudomonas and "yeast rods." On the twenty-fourth hospital day the infant developed hyperpnea with increased cyanosis and died. Terminally her temperature rose to 103°F (rectal).

Discussion

The sudden onset of semicoma, decerebrate posture, bilateral spasticity and pyramidal tract signs, forced grasp and suck reflexes, as well as the electroencephalographic findings, point to a diffuse encephalopathy. The absence of papilledema or separation of the sutures in the skull x-ray film speak against an underlying chronic process, such as hydrocephalus or a space-occupying lesion. Arterial thrombosis would be expected to present with more focal and asymmetrical signs than were observed in this patient. Neither a venous thrombosis nor a gross cerebral hemorrhage is consistent with the patient's course and the findings on examination of the cerebrospinal fluid (CSF). Although terminally the patient apparently developed a generalized sepsis, a bacterial infection of the central nervous system at the time of admission would seem to be remote in view of the CSF findings, the supple neck and the failure to respond to antibiotic therapy. However, because of her initial febrile response and since a repeat examination of the cerebrospinal fluid was not performed, an infectious process in the central nervous system cannot be ruled out. A viral cause for the encephalopathy would also be unlikely in view of the CSF findings, although this supposition is less certain. Unfortunately, serial virus titers of the serum were not obtained.

In view of the chronic state of hypoxia which was present throughout the life of this patient and in whom several bouts of hypoxia attributed to bronchiolitis and pneumonitis had occurred, diffuse hypoxic changes in the brain would be anticipated. However, there remains the question of what had caused the sudden onset of semicoma, decerebrate rigidity and the progression of neurological findings which led to her death. An acute hypoxic episode superimposed on an already marginally oxygenated (and presumably acidotic) brain would certainly be compatible with the patient's course. The exact cause of this hypoxic event is, however, from a clinical point of view, indeterminate. Because of the changing intensity of the shunt murmur, however, obstruction to pulmonary flow at the anastomotic site may be considered to be a possible cause of this. An alternate possibility, despite the lack of evidence for infection, is the exquisite vulnerability of the hypoxic brain to viral, bacterial, or fungal invasion.

Autopsy findings

The heart was increased in size (Fig. 1). The right atrium was enlarged and its



Fig 1 Photograph of the formalin-fixed gross heart The cut to the left exposes the blind right ventricle that to the right the hypertrophied left ventricle A probe has been placed in the site of the surgical anastomosis between the aorta and the pulmonary artery

wall was thickened It received the venae cavae and coronary sinus in a normal manner There was a fossa ovalis defect measuring 0 5 cm in greatest dimension No definite tricuspid orifice was seen The right ventricle was a minute chamber with a tremendously thickened wall a markedly thickened endocardium and no definite outlet. The proximal portion of the pulmonary artery was identified as a minute almost blind sac The left atrium was enlarged and its wall was thickened It received the pulmonary veins in a normal manner The mitral orifice was enlarged but the mitral valve was normally formed The aorta emerged from this chamber through an enlarged orifice and a normally formed aortic valve There was a patent anastomosis measuring 3 mm between the aorta at the end of its ascending portion and the distal portion of the main pulmonary artery No vegetations were observed either at the site of anastomosis or on any of the valves. The ductus arteriosus was closed The gross diagnosis here is tricuspid atresia without transposition with nonfunctioning right ventricle and surgical anastomosis between the aorta and the main pulmonary artery

The lungs showed pulmonary edema No significant pulmonary infection was found on microscopic examination

The external surface of the brain showed a generalized congestion of the small pial vessels without gross evidence of meningitis. There was no evidence of flattening or herniation nor were any thrombi demonstrated in the dural sinuses. The fixed brain was studied by serial coronal sectioning This revealed areas of focal destruction in white matter scattered throughout both hemispheres (Fig 2) The overlying cortex appeared grossly to be normal and there was sparing of the arcuate fibers for the most part The corpus callosum was not involved and the ventricles were not dilated

On microscopic examination the lesions in the white matter were found to consist of extensive areas of tissue destruction with numerous glia and macrophages (Fig 3) In general the arcuate fibers were spared and there were also occasional preserved islets of myelinated fibers, which were often perivascular in position The silver impregnations showed a relative preservation of the nerve fiber network At the periphery of the lesions, foci of basophilic calcific like material were found (Fig 4) These consisted of dense rod like and spherical structures They were some



Fig 2 Coronal section of the formalin-fixed brain.



Fig. 3. Celloidin section from an involved area stained by the Luxol fast blue–PAS–hematoxylin technique. The arrow points to the granulomatous lesion shown in Fig. 5.

times moderately periodic acid-Schiff (PAS) positive, and with the Von Kossa technique only a few darkened areas were seen. The white matter adjacent to the lesions also showed a rather marked astrocytosis.

The blood vessels generally were congested but no thrombi could be demonstrated. In the cerebral cortex there were a few areas of infarction with activation of microglia. Foci of astrocytosis were also seen, but the most prominent feature in gray matter was the presence of fairly numerous granulomatous lesions (Fig. 5). These lesions contained organisms which stained positively with the PAS technique and had the general morphology of *Candida albicans*. Similar lesions also containing organisms were found in the myocardium (Fig. 6) and in the kidney.

The hippocampus showed loss of nerve cells with some microglial activation in Sommer's sector, together with a status spongiosus of the underlying white matter. Although the cerebellum showed several focal areas of infarction involving the molecular layer with complete loss of Purkinje cells, no generalized loss of these cells was demonstrated.



Fig. 4. Paraffin section of white matter adjacent to the areas of destruction stained by the hematoxylin-eosin technique.

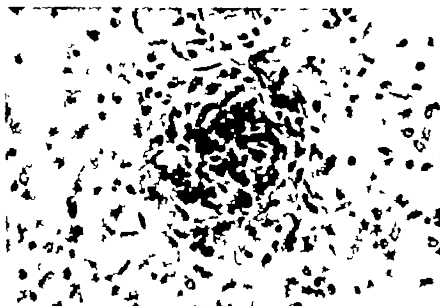


Fig. 5. High-power microphotograph of the cortical lesion shown in Fig. 3.



Fig. 6. Paraffin section of heart stained by the PAS-hematoxylin technique. The arrow indicates the fungal organisms.

Interpretation and correlations

The first question to be considered is the nature of the major change in the brain namely the necrosis of white matter The rather massive involvement suggests a diagnosis of a form of leukodystrophy Against this is the fact that the destruction of myelin was incomplete within the lesions. Banker and Larroche[1] have recently described destructive lesions in the brains of infants. The common factor in all their cases was the presence of one or more episodes of hypoxia and the lesions were attributed to this. Several cases of congenital heart disease were included In the newborn infants the cerebral lesions were periventricular in location, but when the hypoxic episodes occurred after the age of 2 weeks areas of subcortical necrosis were found Although none of these reported cases showed lesions as extensive as those in our case It is our opinion that this case belongs in the same category and that it is anoxic in nature. Areas of necrosis of white matter with very little demonstrable cortical change have been produced experimentally in adult cats.[2] Two procedures were necessary first, ligation of the basilar artery (producing presumably a state of relative cerebral anoxia) and secondly ligation of the common carotid artery at a later time. Similar lesions have also been described in young human adults after carbon monoxide poisoning [3]

A second point which must be considered is the causal relationship between the two types of lesions seen in the brain. In this we may be aided by another case obtained from Dr Orville T Bailey This was the case of a 3½-year-old white girl who entered the hospital with symptoms of increased intracranial pressure of 1 week's duration An exploration of the posterior fossa performed on the fourth hospital day was negative. Her course was gradually downhill and in spite of a subtemporal decompression and a ventriculo-atrial shunt, she died 2 months after the exploration At autopsy the brain showed disseminated granulomas of the cerebral cortex (Fig 7) These were found to contain organisms morphologically identical with those observed in our case In spite of the much greater cortical involvement than in our case accompanying necrosis of white matter was not seen This case demonstrates that there is no necessary direct causal relationship between the cortical granulomatous lesions and necrosis of white matter in our case

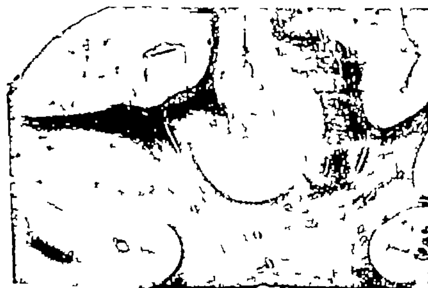


Fig 7 Celloidin section of brain stained by the Kluver technique

The type of heart lesion in our case was such that death would have been anticipated with closure of the ductus arteriosus had surgery not been performed. The type of surgical repair attempted was, in so far as we know, unique. In spite of the fact that oxygenation of tissues was noted to be improved at the time of operation, the pulmonary flow remained inadequate and the patient was observed to have severe intermittent hypoxic episodes prior to the catastrophic event which led to her final hospitalization. The morphologic manifestations of these earlier events are considered to be the "calcified" lesions, the hippocampal changes, and the focal cortical infarctions described above. The massive lesions of the white matter could then be viewed as the result of a single severe hypoxic event *occurring just prior to her* final hospitalization in a brain already in a state of chronic oxygen deficiency. In this interpretation, the disseminated fungus infection would be viewed as a terminal event and probably the immediate cause of death.

As to the cause of the postulated single severe anoxic event which led to this patient's death, it was suggested on the clinical evidence of a change in the cardiac murmur that an obstruction to blood flow occurred at the anastomotic site, the single source of pulmonary flow. At autopsy, however, no such lesion was demonstrated. It is also possible, but not likely, that the fungus infection was present at the time of her final admission and that a shower of emboli was responsible for the anoxic event. The fact that leukomalacia was not present in the second case cited does not rule this out, since that infant was not in a state of chronic hypoxia. In favor of this interpretation is the presence of organisms in the heart; against it is the fact that the granulomatous lesions in the brain were confined to the gray matter and were all relatively acute. Although it is possible that some of the "calcified" lesions described above are pseudomycelia, the fact that such lesions were also found in the cases of Banker and Larroche, in which no fungal infection was known to be present, leads us to also reject this interpretation.

The occurrence of intermittent hypoxic episodes in cyanotic heart disease with decreased pulmonary flow is a well-recognized clinical entity, sometimes designated as the "spell syndrome."[4] It has long been suspected that the cause of these episodes is related to a decrease in systemic resistance. In a recent study,[5,6] physiologic data supporting this idea were presented and the role of acidosis as an initiating event was emphasized. Although direct evidence is lacking, it is entirely possible that an acid-base imbalance associated with hyperpnea and increased right-to-left shunting initiated the final hypoxic event in our patient. In view of all the evidence, it is our opinion that this is the most likely *interpretation of the course of events in* our patient.

Summary

A case of tricuspid atresia with surgical intervention has been presented. The infant died after what appeared clinically to be an episode of acute hypoxia. At autopsy, the brain showed two very unusual lesions, massive necrosis of white matter and disseminated fungal granulomata. The evidence that the first of these is an anoxic lesion is reviewed. The second is considered to be a terminal event.

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Fundamentals of clinical cardiology

Aortic valve replacement with the Starr Edwards ball-valve prosthesis

Indications and results

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Three years have elapsed since the introduction of the present Starr Edwards ball-valve aortic prosthesis.[1,2] It is now used in many institutions.[3-8] Indeed valve replacement with this or other recently developed prostheses has become the surgical treatment of choice for patients with calcific aortic valve disease or aortic regurgitation The rapid acceptance of valve replacement has occurred largely because of the long term effectiveness of prostheses when compared to earlier surgical approaches.[9] Furthermore as experience is gained the mortality rate for valve replacement has steadily declined to a very acceptable range It is the purpose of this report to discuss the early and longer term results and complications of aortic valve replacement with the Starr Edwards prosthesis. This information will then lead to a consideration of present indications for surgery

A total of 86 patients underwent isolated aortic valve replacement on the resident s teaching service at this institution in the years 1962 through 1964 Six more patients underwent surgery with a prototype valve in 1961 but these will not be included in the present series. All patients who had multiple valve surgery were excluded Eighty-one of the 86 patients had isolated aortic valve disease. There were 12 early deaths and 9 late deaths which produced a total mortality rate of 24 per cent (Table I) However the total mortality rate fell to 13 per cent in 1964 and continued to decrease in 1965 A total mortality rate of 4 per cent was obtained by the same team of surgeons at a private Portland hospital in 1964 A detailed postoperative follow up of more than 6 months duration is available for 50 of the 65 survivors. Distribution of the follow-up interval is listed in Table II All follow-up information was collected through May 1965

Immediate operative results and complications

Table III shows the average cardiac index before and after operation in 9 patients who underwent aortic valve replacement The cardiac index rose promptly

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Table I Early and late mortality rates for aortic valve replacement

Year	Number of operations	Early deaths	Per cent	Late deaths	Per cent	Total deaths	Per cent
1962	16	2	12	3	19	5	31
1963	38	8	21	4	11	12	32
1964	32	2	6	2	6	4	13
Total	86	12	14	9	10	21	24

Table II Duration of postoperative follow-up in 50 patients after aortic valve replacement

Duration (months)	Number of patients
6 12	24
12 18	9
18 24	11
More than 24	6
Total	50

*Table III Average change in cardiac index after aortic valve replacement in 9 patients**

	Time			
		Postoperative		
	1 Day preop	Day of operation	Day 3	2 3 Week
Cardiac index (L/min M²)	1 9	2 6	3 1	3 3

*Cardiac index determined by radioiodine dilution with precordial scanning.[26]

after operation This contrasts sharply with the findings in patients undergoing mitral valve replacement who often have a low cardiac index for several days after operation [18] In general the postoperative course of patients with aortic valve replacement is far less complicated than that of patients with mitral valve replacement [11]

The causes of early deaths are listed in Table IV Early mortality was in no way related to the preoperative age or severity of the disease The remarkably benign postoperative course in many severely ill patients has led us to consider that no patient who has hemodynamically significant aortic valve disease is inoperable on the basis of the valve disease alone Coronary artery disease is not necessarily considered to be a contraindication to surgery although 2 patients who died of ventricular fibrillation had significant coronary artery disease The type of aortic valve lesion did not affect the operative risk

Two deaths early in this series occurred when cardiopulmonary bypass could not be discontinued because of untreated mitral valve disease Such patients now undergo double valve replacement.[13] Another patient who had an untreated coarctation of the aorta nearly died of pulmonary edema in the early postoperative period It has been our experience that the operative risk is high if a significant hemodynamic abnormality is left untreated presumably because some left ventricular myocardial depression occurs even after the most careful cardiopulmonary bypass

Long-term results

Long term results of Starr Edwards aortic valve replacement have been extremely gratifying Valve replacement has a great advantage over earlier procedures because immediate hemodynamic gains are maintained Although the maximum follow up period is still only 3 years, there is no evidence to suggest that the good results from surgery will not be maintained for an indefinite period

The 50 patients in whom a detailed

follow up of 6 months or longer is available are representative of the entire group of 86 patients who underwent operation. The etiology of the aortic valve disease for these patients is listed according to the type of lesion in Table V. It is notable that a congenital abnormality of the aortic valve was thought to be the etiology in most instances. This was determined from the history and by the appearance of the valve at the time of operation. As more and more patients with isolated aortic valve disease undergo surgery it has become apparent that the traditional belief that rheumatic endocarditis is the most common cause of such a lesion is not correct.[13,14]

Table IV. Causes of early and late deaths after aortic valve replacement

Cause	*Number of patients*
Early deaths	
Ventricular fibrillation	4
Technical problems	4
Untreated mitral valve disease	2
Left ventricular failure	1
Cerebrovascular accident during bypass	1
Total	12
Late deaths (2 months or later)	
Thrombosis around prosthesis	4
Coronary artery disease	2
Erosion of aortic root by prosthesis	1
Bacterial endocarditis	2
Total	9

The average preoperative hemodynamic data for the 50 patients are listed in Table VI. The figures indicate that considerable hemodynamic abnormality was present, and that those with mixed stenosis and regurgitation had the greatest disability. Of note the patients with pure aortic stenosis (no diastolic murmur) had minimal cardiac enlargement. Cardiac enlargement was estimated from a method and nomogram derived from the work of Schwarz.[15] This involves calculation of the frontal heart area on a standard 7 foot postero-anterior chest x-ray film. The calculated frontal heart area is then compared to a predicted normal value for a patient of that size and the difference is expressed as a percentage deviation from the expected normal. By this method we define mild cardiac enlargement as a frontal heart area of +10 to +30 per cent of predicted, moderate cardiac enlargement ranges from +30 to +45 per cent, and gross cardiac enlargement is present if the predicted area is greater than +45 per cent. The largest heart encountered in this series was +100 per cent. In such a heart left ventricular volume may be four times normal.

Table V. Etiology of aortic valve disease in 50 patients

Lesion	*Etiology*				*Total*
	Rheumatic	*Congenital*	*Unknown*	*Aortic root disease**	
	(Number of patients)				
Pure aortic stenosis	1	1	4	0	17
Aortic stenosis and regurgitation	2	1	3	0	1
Pure aortic regurgitation	7	4	1	4	16
Total	10	28	8	4	50

*Includes 2 patients with cystic medial necrosis, 1 with syphilitic aortitis and 1 with idiopathic dilatation of the aorta.

Resting left ventricular end-diastolic pressure was elevated in half of the patients and systemic blood flow was subnormal in 80 per cent. The adequacy of systemic blood flow was estimated from the systemic arteriovenous oxygen difference and considered to be abnormal if this value exceeded 5.1 volumes per cent.[18] The age of those with aortic stenosis was generally greater, the eldest being 74 years.

Postoperative hemodynamics. An earlier report from this laboratory presented preoperative and postoperative cardiac catheterization data in 18 of the early cases in this series.[17] All of these patients exhibited significant hemodynamic improvement after operation but the restoration of completely normal hemodynamics both at rest and during exercise was not usual. This was also noted by Judson and co-workers.[18] Three examples of patients who had excellent surgical results are presented in Figs. 1-3 and Table VII. Case 1 had pure aortic regurgitation. Case 2 had combined stenosis and regurgitation and

Table VI. Preoperative hemodynamic data in 50 patients

Lesion	Number of patients	LV pressure (mm. Hg)	Cardiac index (L./min./M.²)	Peak systolic gradient across aortic valve (mm. Hg)	Age (yr.)	FHA increase (%)
Pure aortic stenosis	17	202/13	2.65	83	51	22
Aortic stenosis and regurgitation	17	218/20	2.36	87	45	45
Aortic regurgitation	16	130/15	2.72	0	40	42

FHA increase: Percentage increase in predicted normal frontal heart area calculated from standard posteroanterior chest x-ray film by the method of [illegible].[16]

Table VII. Preoperative and postoperative hemodynamics in 3 patients with different types of

Patient	Functional class	ECG	Increase of frontal area (%)			Heart rate (beats/min.)	Cardiac index (L./min./M.²)
Case 1, 51 yr., M, AR	IV	LVH‡	63	Preop.	Rest	72	2.65
	I	NL	8	Postop. 2 mo.	Rest Exercise	76 96	2.60 4.40
Case 2, 51 yr., M, AS-AR	III	LVH	20	Preop.	Rest	64	2.50
	I	NL	10	Postop. 6 mo.	Rest Exercise	71 86	3.70 4.05
Case 3, 56 yr., F, AS	III	LVH	89	Preop.	Rest	72	1.90
	II	ST-T abnormal only	27	Postop. 11 mo.	Rest Exercise	78 112	3.00 3.80

*Determined by indocyanine green dilution.
†Calculated from cardiac index and oxygen consumption.
‡Left ventricular hypertrophy. See text for definition.[19,20]
LV, Left ventricle; BA, Brachial artery; LA, Left atrium; SV, Stroke volume; EDV, End-diastolic volume; NL, Normal; [illegible]

Case 3 had pure stenosis preoperatively. Left ventricular end-diastolic volume and left ventricular emptying ratio (stroke volume/end-diastolic volume) were measured by the thermodilution technique in the postoperative study.[19,20] The normal left ventricular end-diastolic volume by this technique is 90 to 135 ml. per square meter and the normal left ventricular emptying ratio is 35 to 55 per cent.[19-21]

Case 1 had gross cardiac enlargement preoperatively and a normal-sized heart postoperatively. Left heart pressures and systemic blood flow were abnormal preoperatively and normal both at rest and during exercise postoperatively. The resting left ventricular end-diastolic volume was restored to normal but the left ventricular emptying ratio was still subnormal. This has been considered by some investigators to be one of the earliest signs of abnormal ventricular performance.[22,23]

Case 2 also had preoperatively a greatly increased resting left ventricular end-diastolic pressure which was restored to normal. However, the increment of cardiac index with exercise in the postoperative study was inadequate according to the standards of either Wade and Bishop[24] or Harvey and associates.[25] In addition, left ventricular end-diastolic pressure rose to an abnormal level during exercise. Since the left ventricular emptying ratio was excellent, these abnormalities may well have been the result of residual left ventricular hypertrophy. Ventricular hypertrophy can decrease ventricular diastolic distensibility and thereby increase ventricular filling pressure and restrict stroke volume.[26]

Case 3 had the largest preoperative heart size in the group with pure aortic stenosis. Postoperatively, the heart has remained slightly enlarged by roentgenogram, but left ventricular end-diastolic volume is within the normal range. This suggests that residual left ventricular hypertrophy was also present in this patient. Preoperatively, the resting cardiac index was greatly reduced. The resting left ventricular emptying ratio was subnormal postoperatively, but all other resting hemodynamic parameters were normal. During exercise, however, the rise in cardiac index was subnormal, and left ventricular end-

aortic valve disease

Oxygen consumption (ml./min./M²)	Arteriovenous oxygen difference (vol. %)†	LV (mm. Hg)	BA (mm. Hg)	LV-BA gradient (mm. Hg)	LA (mm. Hg)	SV (ml./M²)	SV/EDV	LV EDV (ml./M²)
149	5 6	100/28	135/40	—	11	37	—	—
118	4 5	125/1	110/70	15	3	34	31	110
262	6 0	170/4	145/90	25	3	46	29	158
145	5 8	194/28	132/32	6	14	39	—	—
136	3 7	125/8	95/60	30	4	52	52	100
369	9 1	182/18	162/80	20	9	47	55	85
140	7 4	233/4	170/67	113	5	26	—	—
137	4 6	150/13	140 68	10	6	39	30	130
331	9 0	192/17	192/96	0	16	34	38	89

[illegible] regurgitation. SS Pure aortic stenosis. [illegible] R Aortic stenosis and [illegible]



Fig. 1. Case 1. Preoperative (*left*) and postoperative (*right*) chest x-ray films. See text.



Fig. 2. Case 2. Preoperative (*left*) and postoperative (*right*) chest x-ray film. See text.

diastolic pressure and left atrial pressure rose to an abnormal level.

Each of these cases must be considered to show an excellent result, since Cases 1 and 2 were asymptomatic and Case 3 had only mild exertional dyspnea. All had angina pectoris, which disappeared after operation. Yet entirely normal hemodynamics were restored in none. This is perhaps to be expected, because in most of the patients currently operated upon left ventricular hypertrophy has been present for many years, and some myocardial damage is likely to have resulted. It is also possible that more than 6 months (the usual time of postoperative catheterization studies in the earlier report from this laboratory and that of Judson and associates[17,19]) is required for left ventricular hypertrophy (and the abnormal dynamics



Fig 3 Case 3 Preoperative (*left*) and postoperative (*right*) chest x-ray films. See text.

it may produce) to regress. The frontal heart area in Case 2 eventually fell from +10 to −12 per cent, and the patient was able to perform heavy physical labor without symptoms. Case 1 who had the most nearly normal postoperative hemodynamic result, was studied 2 years after operation

The systolic pressure gradient across the prosthesis noted in these three cases is typical of that usually encountered.[17,18,27] Resting peak systolic gradients have averaged 20 mm Hg between the left ventricle and brachial artery [17] The size of the gradient is not related to the size of the prosthesis.[17] The gradient usually decreases with exercise suggesting that the critical area of stenosis is the space between the ball and the aortic wall. The prosthesis has thus been altered to make the cage longer and take advantage of the post stenotic dilatation of the aorta that is present in many of these patients. Pressure gradients in cases studied since this revision have been of lesser magnitude Whether the small systolic pressure gradient across the prosthesis may be responsible for the persistence of some hemodynamic abnormalities is not known but the size of the pressure gradient across the prosthesis has borne no relationship to the clinical result

Postoperative heart size Twenty-seven of the 50 patients (54 per cent) had a normal frontal heart area after operation. Preoperatively 20 of these had cardiac enlargement ranging from +10 to +78 per cent of predicted Postoperatively the frontal heart size was reduced to +10 to +20 per cent in 7 more patients. Thus, surgery produced a return to normal or nearly normal heart size in 34 of 50 patients (68 per cent) a remarkable figure In most instances, most of the eventual reduction in heart size had occurred by 6 months, but further reduction in heart size up to 18 months after operation has been documented

The heart size remained significantly increased (greater than 20 per cent increase in predicted frontal heart area) in 16 patients (32 per cent) although it was significantly reduced in half of these Six of these patients had regurgitation around the prosthesis, but in only one was the regurgitation thought to be of enough magnitude to entirely account for the cardiac enlargement. At least 3 patients had coronary artery disease and this was suspected in 3 others One had a thrombosis around the prosthesis with resultant aortic stenosis, and one had a residual coarctation of the aorta. No specific explanation could be advanced in the remainder of the patients, except that massive left ventricular dilatation of long

standing (+64 +70 and +89 per cent) was present preoperatively in 3 of them.

Thus if no complicating factor is present after operation and gross cardiac enlargement has not been of long duration it is reasonable to expect that normal or nearly normal heart size will be restored by aortic valve replacement. The heart will return to normal size in nearly all patients with aortic stenosis. Most of the unexplained failures occur in patients with aortic regurgitation or mixed stenosis and regurgitation. In such patients anatomic rearrangement of the left ventricular musculature may have developed which precludes a return of the heart to normal size.[11]

Symptoms and functional class. Classification of patients with aortic valve disease according to the New York Heart Association Functional Classification I through IV is notoriously difficult because of the symptoms of angina pectoris and syncope. Patients who are otherwise able to perform considerable physical activity may on occasion develop syncope. Others may experience angina only with rather marked exertion. Finally digitalization may convert a Class III or IV patient to Class II. In determining the preoperative functional classification we have based our judgment largely on the symptoms of the patient at the time of cardiac catheterization. At that time the benefits of medical management were usually maximal. Thus, several Class II patients preoperatively had had more serious symptoms in the past and may well have been regarded as Class III or IV patients in other institutions.

Table VIII lists the preoperative and postoperative functional class for the 27 patients in whom postoperative heart size was normal and the 23 with persistent cardiac enlargment. Most were severely disabled preoperatively and there was no difference between the two groups. However there was a difference postoperatively. The patient in whom heart size returned to normal was usually without symptoms, whereas the patient with persistent cardiomegaly usually had mild symptoms of exertional dyspnea and or fatigability.

Thirty-four patients had angina pectoris preoperatively and this disappeared in all but 2 who were known to have coronary artery disease. No patient required diuretic therapy after operation except the 2 who eventually died. Similarly orthopnea paroxysmal nocturnal dyspnea and syncope disappeared in all but these 2 patients.

Table VIII. Change in symptoms after aortic valve replacement

Patients	*Functional class*	*Preop*	*Postop*
With normal heart size after operation	I	1	22
	II	7	4
	III	13	0
	IV	6	0
	Angina	20	1
With abnormal heart size after operation	I	0	6
	II	6	16
	III	12	1
	IV	3	1†
	Angina	14	1*

*Patient had angina and became class III after myocardial infarction 6 months postoperatively. At autopsy extensive coronary disease was present.

†Patient died 6 months postoperatively of aortic stenosis secondary to extensive clot formation around prosthesis.

In general 6 months were necessary for the full benefit from surgery to occur. However in younger patients this was reached at 3 to 4 months whereas in older patients 6 to 9 months were required. We have imposed no restrictions on activity after full recovery other than to have the patient avoid heavy lifting. Many patients have been able to return to jobs requiring considerable physical exercise. Nearly all have been able to return to work although only light work has been tolerated in several patients with residual cardiomegaly.

The electrocardiogram. Electrocardiographic changes occurring after surgery are listed in Table IX. Left ventricular hypertrophy[41,29] disappeared in 19 of 25 patients (76 per cent) with a normal sized heart postoperatively but disappeared in only 7 of 20 patients (35 per cent) who had residual cardiomegaly. In 16 of 20 instances of persistent left ventricular hypertrophy the QRS amplitude decreased. Nine patients developed entirely normal electrocardiograms. The persistence of evidence of left ventricular hypertrophy on the

*Table IX. Change in the electrocardiogram after aortic valve replacement**

Patients	ECG diagnosis	Preop	Postop
With normal-sized heart after operation	LVH	25	7
	ST-T abnormality only	0	8
	Increased QRS amplitude only†	0	3
	Normal	1	8
With enlarged heart after operation	LVH	20	13
	ST-T abnormality only	0	6
	Increased QRS amplitude only†	0	1
	Normal	1	1

*Three patients with bundle branch block preoperatively are not included.

†Defined as greatest R + greatest S in precordial leads more than 45 mm., but ST and T waves normal.

LVH, Left ventricular hypertrophy. For this diagnosis an ST and T abnormality had to be present, and the greatest R + greatest S in precordial leads was more than 45 mm.[39,40]

electrocardiogram of many patients with a normal-sized heart after surgery is consistent with the hypothesis that permanent abnormality of the left ventricular myocardium may result from left ventricular hypertrophy of long duration.

The electrocardiographic abnormalities returned toward normal more slowly than did the heart size. It is likely, therefore, that the electrocardiogram will eventually become normal in several patients with normal-sized hearts in whom it was still abnormal at the time of the 6-month follow-up.

Long-term complications

Systemic arterial embolism. This represents the principal long-term complication of aortic valve replacement. Table X lists the incidence of systemic embolism for the entire series. Coronary embolism was the cause of death in 3 patients and thrombosis around the prosthesis produced fatal aortic stenosis in another. Thus 4 of 8 late deaths were due to the formation of thrombus around the prosthesis. The other 11 incidents of suspected embolism have been nonfatal and in all but one instance there has been no significant residual. Three patients had 2 embolic incidents. Only one embolus occurred in the group of patients who did not have calcific disease. Although epithelialization of the sewing ring has usually taken place by 6 months after operation, emboli may occur subsequently. Eight of the 15 embolic episodes (53 per cent) occurred after 6 months—in one instance 2 years after surgery.

Nine of 15 emboli (60 per cent) occurred in patients receiving therapy with oral anticoagulant drugs. The usefulness of such drugs in preventing emboli in patients with aortic prostheses is not yet established and in many centers these drugs are not used.[3,4,6] It is possible that platelet emboli may be responsible for many embolic incidents in these patients,[21,22] and at present there is no suitable agent to prevent this type of embolism.[22] Furthermore, some investigators have suggested that inadequate control with oral anticoagulants may produce a state of "hypercoagulability."[24]

It has been our impression that the resolution of the thromboembolism problem lies in the production of a prosthesis that possesses antithrombotic properties, rather than in anticoagulant drugs. Nevertheless, we use anticoagulant drugs in all patients who do not have a disease that contraindicates their usage.

Regurgitation around the prosthesis. Table XI shows the incidence of basal diastolic murmurs in the 74 patients who sur-

Table X. Incidence of systemic embolism after aortic valve replacement in 86 patients

Year	Number of operation	Number of patients having emboli	Per cent	Number of fatal emboli	Per cent
1962	16	3	19	0	0
1963	38	7	18	3	8
1964	32	5	16	1	3
Total	86	15	17	4	5

Table XI. Incidence of a basal diastolic murmur in 74 patients who survived the early postoperative period

Year	Number of patients	Number of patients with murmurs	Per cent
1962	14	4	29
1963	30	7	23
1964	30	8	27
Total	74	19	26

vived the immediate postoperative period. The incidence is similar for all 3 years. In the 19 patients with a murmur the presumed leak around the prosthesis was judged to be of no hemodynamic significance in 9. These patients had a normal sized heart and no peripheral signs of aortic regurgitation. In the other 10 cases the heart size remained abnormal postoperatively although it was significantly decreased by surgery in half of these. Whether the regurgitation was of significant magnitude to account for the residual cardiomegaly has not always been clear since the peripheral blood pressure was normal in most of these. Reoperation has been required in only 3 cases.

The basal diastolic murmur was usually noted within 3 weeks after operation (12 instances) but appeared from 4 to 6 months postoperatively in 7. The patient who died as a result of massive thrombosis around the prosthesis had a murmur at 2 months, and this murmur disappeared at 4 months.

Hemolytic anemia. Hemolytic anemia has occurred postoperatively in 5 patients. In 2 instances the process was transient and responded to adrenal steroids. In 3 cases the hemolysis was demonstrated to be intravascular and responded only to iron supplement. Regurgitation around the prosthesis was present in each case and it is thought that excessive turbulence of the blood produced traumatic destruction of red cells in these patients.[24] Red cell survival time by the chromium 51 method was less than 16 days in all 3 patients.

Studies from this institution have shown that many patients with aortic valve disease have a variable degree of intravascular hemolysis.[25] Many patients continue to have a shortened red cell survival time after the implantation of a Starr-Edwards prosthesis but in many the red cell survival time is normal. The average red cell survival time in 9 patients with no regurgitation around the prosthesis postoperatively was 22.4 days compared to an average of 20.2 days in 13 patients preoperatively (Table XII). In 6 patients, red cell survival time was studied both before and after surgery. It increased in 5 in whom no leak was present and decreased in 1 patient who had a leak around the prosthesis. Thus the Starr-Edwards prosthesis has *less tendency* than the pre-existing lesion to produce red cell hemolysis. However if regurgitation occurs around the prosthesis a severe hemolytic anemia may occur.

Bacterial endocarditis. Since the beginning of this series all patients have received prophylactic oxacillin for 3 months after operation (when not allergic) and vigorous measures have been carried out to prevent staphylococcal contamination in the surgical suite and recovery room. As a result bacterial endocarditis has not been a frequent complication. Only one patient died of staphylococcal endocarditis. Another patient died of Pseudomonas endocarditis secondary to an infection of the urinary tract.

Indications for surgery

The results of aortic valve replacement in this series indicate some disadvantage if only patients with far-advanced symptoms are operated upon. Nearly half of the survivors will retain some cardiac enlargement. In those who have a normal sized heart after surgery there is usually not a return to entirely normal hemodynamics in spite of an excellent clinical result. Perhaps longevity may be compromised in those with persistent cardiac enlargement. Better results would undoubtedly be obtained if patients were operated upon soon after symptoms appeared or even if some *asymptomatic* patients with hemodynamically significant disease were operated upon. However the

*Table XII Red blood cell survival before and after aortic valve replacement**

	Number of patients	Red cell half life (days)	Range
Preoperative			
Aortic stenosis	5	21 9	16 5–25 0
Aortic stenosis and regurgitation	6	18 8	14 0–23 5
Aortic regurgitation	2	20 5	18 5–22 5
Total	13	20 2	
Postoperative†			
No leak	9	22 4	18 0–27 5
Leak	4	16 8	9 5–22 5
Paired comparisons			
Preoperative	5	18 8	14 0–22 0
Postoperative (no leak)	5	24 2	19 5–27 5

*Red cell survival determined by Cr^{51}. Normal red cell half life is 24 to 28 days.
†Only 5 of the preoperative patients studied are included in this group. For the other 8 patients there were no preoperative studies.

current total mortality rate and incidence of postoperative complications still does not justify valve replacement in most asymptomatic patients. There are, however, certain exceptions. To help define the exceptions, a preoperative hemodynamic study is required.

We recommend left heart catheterization in nearly all *symptomatic* patients with suspected aortic valve disease, not only to assess the severity of the aortic lesion but also for reasons mentioned earlier to evaluate any other lesion which might be present. This information is also crucial in the evaluation of postoperative results. If there are no symptoms catheterization is recommended if there is cardiac enlargement or evidence of left ventricular hypertrophy on the electrocardiogram. A more liberal policy *is adopted* for younger patients with suspected aortic stenosis.

We do not routinely attempt coronary angiography because in our experience severe aortic valve disease and severe coronary artery disease rarely coexist. Mild coronary disease of course is not a contraindication to surgery. In the older patient who may have serious pulmonary, renal or generalized vascular disease detailed preoperative studies are necessary. In such patients, aortic valve replacement may not be expected to materially affect the long term prognosis, and if this is judged to be the case surgery is not warranted.

The indications for aortic valve replacement must be tailored to the type of aortic valve lesion. Although the operative risk is independent of the type of lesion significant differences in natural history and hemodynamic defects exist between aortic stenosis and aortic regurgitation which necessitate different considerations.

Aortic stenosis Takeda and co-workers[38] studied the natural history of aortic stenosis after symptoms had developed. Their results were similar to those reported in earlier studies.[77,78] These investigators found that the average time interval from the onset of any symptom to death was 4 7 years. The average age at death was 62 5 years. Angina pectoris and syncope were usually early symptoms. Congestive heart failure occurred late, and was the cause of death in half of the patients. These authors found a 6 per cent incidence of sudden death in this group of symptomatic patients. A similar incidence of sudden death may occur in relatively asymptomatic younger individuals—not all of whom have evidence of significant aortic stenosis by clinical criteria.[4,49]

It is generally agreed that a peak systolic pressure gradient of 50 mm. Hg across the

aortic valve (when cardiac output is normal) or a calculated aortic valve area of less than 0 75 cm per square meter represents hemodynamically significant aortic stenosis, and places the individual in the group with a risk of sudden death[39-42]

When the poor prognosis of symptomatic aortic stenosis is considered we have felt justified in recommending aortic valve replacement to any symptomatic patient who has significant aortic stenosis. We also recommend surgery to asymptomatic patients who have a peak systolic gradient of more than 70 mm Hg across the aortic valve Close questioning will often reveal that such patients are not truly asymptomatic

Young people with hemodynamically significant aortic stenosis represent a unique problem They are often asymptomatic and there is usually no calcification of the aortic valve. It has been our policy to attempt open commissurotomy in such cases if a tricuspid aortic valve is present If an adequate result cannot be obtained then the valve is replaced Only long term follow up will determine how many young people who undergo aortic valve commissurotomy will later require valve replacement but at present we have not thought that routine valve replacement in this group is justified

Pure aortic regurgitation When compared to patients with aortic stenosis, patients with pure aortic regurgitation have fewer symptoms and larger hearts. In aortic regurgitation left ventricular dilatation is a fundamental and early expression of the disease The prevention of irreversible changes which may occur in dilated hearts must be a strong consideration in these patients. In this regard half of the patients in the present series with frontal heart areas exceeding +25 per cent preoperatively never developed a normal-sized heart postoperatively

As in aortic stenosis, clinical evaluation of the severity of the lesion may be misleading and considerable reliance must be placed upon the results of cardiac catheterization[43] In these patients attention is focused on the effects of the regurgitant blood flow on left heart pressures and cardiac index The exercise response has been extremely useful in this regard Gross abnormalities in left ventricular end-diastolic pressure and systemic blood flow may occur during exercise in patients in whom these parameters were normal or nearly normal at rest[43]

A study by Segal and associates[44] of 83 patients with rheumatic aortic regurgitation demonstrated that the average age at onset of signs of aortic regurgitation was 20 years with onset of symptoms at age 30 and death at age 40 Thus, the course after symptoms appear is longer than that for aortic stenosis but the onset of symptoms occurs at a much earlier age. These workers also found a 5 per cent incidence of sudden death in those with symptoms In another study Bland and Wheeler[45] considered the incidence of sudden death to be higher (25 per cent) once symptoms had appeared[45] These investigators also noted that the appearance of angina pectoris in patients with aortic regurgitation was an ominous sign since most of them died within 2 years after onset

There is no question that Class III or Class IV patients with aortic regurgitation are individuals urgently in need of surgery since profound hemodynamic disability is nearly always present But what of the Class II patient who has significant cardiomegaly minimal hemodynamic abnormalities and may have occasional angina pectoris This is one of the most common types of patient that we have encountered We consider Class II patients who have angina pectoris to be candidates for surgery Other indications include either an abnormal resting systemic blood flow or an elevated resting left ventricular end diastolic pressure (the two findings usually coexist) since both indicate that the lesion is not being well tolerated by the left ventricle.[43] If systemic blood flow and left heart pressures are normal both at rest and during exercise surgery is not recommended unless gross cardiac enlargement (greater than a 35 to 40 per cent increase in frontal heart area) is present In such patients the prevention of irreversible myocardial abnormalities becomes a prime consideration

Aortic regurgitation of rather acute onset is not infrequently encountered This usually is the result of an abnormality of the aortic root or bacterial endocarditis

Such patients may urgently require surgery within a short period of time. In many the aorta must also be repaired. Eight of the 86 patients in the present series had aortic regurgitation of this type.

Mixed aortic stenosis and regurgitation. Patients with combined aortic stenosis and regurgitation merit separate comment. Both a pressure load and a volume load are present when stenosis and significant regurgitation coexist. The law of Laplace, as applied to the heart, indicates that left ventricular contractile force is directly related to both left ventricular pressure and left ventricular cavity radius.[22, 44] Thus, when ventricular dilatation is present a greater contractile force is required to maintain a given ventricular systolic pressure. The left ventricular systolic contractile force requirement may consequently be higher in patients with mixed stenosis and regurgitation than in those with either lesion alone. Since contractile force and not mechanical work is the major determinant of myocardial energy consumption[22, 44-48] and the amount of energy production is limited, these patients with a mixed lesion may have considerable clinical and hemodynamic disability without impressive signs of either aortic stenosis or regurgitation. A patient with a combined lesion who has a systolic pressure gradient of only 40 mm Hg across the aortic valve may indeed have greater demands on the left ventricle than occurs in pure stenosis with a much larger gradient, or pure regurgitation in which left ventricular volume is twice normal.[49] It is important to recognize this and not deny surgery to such patients. In general, however, these patients have the highest left ventricular end-diastolic pressure and lowest systemic blood flow preoperatively and are the most urgent candidates for surgery.

Summary

The results of aortic valve replacement with the Starr Edwards prosthesis are reviewed in 86 patients. The total early and late mortality rate was 24 per cent. This fell to 13 per cent in 1964 and can be expected to decline further. Nearly all survivors are greatly improved by surgery. Detailed follow up of 6 months to 3 years is available in 50 patients. All but one had symptoms prior to operation and hemodynamic study preoperatively demonstrated gross abnormalities in most. Sixty-six per cent became asymptomatic whereas mild limitation to exercise persisted in another 40 per cent. Angina pectoris disappeared in 32 of 34 instances. Sixty-eight per cent had a normal or only slightly enlarged heart after operation. Electrocardiographic evidence of left ventricular hypertrophy disappeared in 58 per cent. Postoperative hemodynamic studies usually demonstrated some mild residual hemodynamic abnormality, probably attributable to irreversible myocardial damage resulting from long standing left ventricular hypertrophy and/or dilatation.

Postoperative complications included regurgitation around the prosthesis, which was rarely of hemodynamic consequence, bacterial endocarditis (rare), traumatic hemolytic anemia (rare), and systemic arterial embolization. Thromboembolism remains the major unsolved problem of aortic valve replacement, and anticoagulant drugs have not been proved to be of value in preventing this.

Indications for aortic valve replacement are discussed in terms of the current mortality rate and incidence of complications, the proved clinical and hemodynamic benefits, and the natural history of the various types of aortic lesions. All symptomatic patients with aortic stenosis, and all Class III or IV patients with aortic regurgitation are candidates for surgery. In addition, surgery is recommended in relatively asymptomatic patients with aortic stenosis who have a transvalvular peak systolic gradient of more than 70 mm Hg, and in those with aortic regurgitation if there is gross cardiac enlargement, angina pectoris, or abnormal left heart dynamics. The possibility of underestimating the hemodynamic severity of a mixed aortic valve lesion was discussed.

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Antianginal drugs.

Part III Clinical use of nitroglycerin

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Nitroglycerin was discovered in 1847 and was first used clinically in 1859. Although its use for angina pectoris is now almost universal, the clinical observations and the experimental studies upon which its use was launched in medical practice would not be acceptable to the modern clinical pharmacologist. Since 1937 it has been known that approximately 75 per cent of all attacks of angina of *effort* end within 2 minutes of cessation of activity and that most patients overestimate the duration of the attack. The evanescence of the untreated attack and failure to separate the therapeutic effect of the drug from that due to simultaneous cessation of effort were crucial factors disregarded in earlier clinical assays.

It is only in the last few years that quantitative studies have been conducted by acceptable methods in investigative therapeutics to evaluate the antianginal efficacy of nitroglycerin. Two recent double-blind quantitative studies conducted independently and made known a few months apart showed that sublingual nitroglycerin was no more effective than a placebo in altering the duration of an attack of exertional angina when given at the onset of pain. In the course of our experimental work on angina, several hundred episodes were treated successfully and without incident with sublingual lactose placebo. If we consider the time sequence between the perception of pain, the search for the nitroglycerin tablet, placement of it under the tongue, its mucosal absorption, and the circulation time to the coronary arteries, one wonders how this agent could be effective in relieving pain which will disappear spontaneously within 2 minutes after effort ceases. For the present, therefore, despite long clinical teaching, the effectiveness of nitroglycerin in the treatment of an established attack of angina of effort must be considered to be unproved. New, well-controlled experiments are needed to further evaluate these findings.

Nitroglycerin is often administered prior to a patient's undertaking of angina-provoking effort (prophylaxis). Opinions as to the efficacy of this maneuver are divided. There are those who contend that nitroglycerin administered 3 to 5 minutes prior to the undertaking of exercise may improve the work performance by 50 to 100 per cent before angina appears. Conversely, similarly well-conducted studies show that only a minority of patients improve their work performance by more than 50 per cent, regardless of pretreatment time. Even in these few patients there is a possibility of bias because of drug recognition, since no perfect nitro-

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glycerin placebo exists. To our knowledge no well-controlled experiments have been conducted to test the efficacy of nitroglycerin either therapeutically or prophylactically in angina provoked by other factors, such as cold weather or emotional disturbance The widespread clinical impression that nitroglycerin is effective in such situations demands that such studies be made.

Thus, theories and conjectures which attempt to explain the antianginal mechanism of action of this drug seem to be premature. A much more pressing problem is the assessment of the situations in which and the degree to which it is effective

It seems to me to be well established that nitroglycerin is a useless drug in the treatment of angina of effort, and that its value in other situations is uncertain Undoubtedly nitroglycerin will continue to be used on clinical grounds in the treatment of various forms of angina. Accordingly the description of its clinical use is still pertinent until these issues are resolved For the treatment of the acute attack, 0 3 to 0 6 mg of nitroglycerin is most commonly administered sublingually In selecting the most appropriate dose of nitroglycerin one should commence with the smallest possible dose and then increase its strength until the patient derives apparent benefit without developing disabling headache. The drug is allowed to dissolve under the tongue, with care being exercised not to swallow the saliva. Some patients can take as many as 30 to 40 tablets per day without harm The vast majority of patients use 1 to 2 tablets per day some require the drug very infrequently Because of the known deterioration of nitroglycerin, a new supply of the drug should be obtained approximately every 3 months.

In the prevention of angina pectoris the common practice has been to recommend that the patient insert a nitroglycerin tablet sublingually prior to undertaking a form of effort known to produce a bout of angina. This can be repeated at intervals as frequent as every half hour Since significant tolerance to nitroglycerin may develop it is logical to interdict treatment every few days in order to allow for return of drug sensitivity

Nitroglycerin has been used orally in either ordinary or sustained release tablets or as a skin ointment for the treatment of angina. There are no adequately controlled studies that attest to the efficacy of these other forms of nitroglycerin therapy in any form of angina

It has been customary to advise patients to sit still and call for a physician if an attack of angina is not relieved within 5 to 10 minutes particularly after the intake of more than 2 nitroglycerin tablets. Whether such pain is always due to an infarction from its inception or whether an anginal attack can be converted into an infarction by hypotension or by coronary blood diversion brought on by nitroglycerin cannot presently be answered If such a sequence of events can even be considered to be possible then nitroglycerin may not be innocuous this possibility adds to the urgency of the need for a better understanding of the role of this familiar drug

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Annotations

Idiopathic nephrotic syndrome in adults

Classification based on histologic criteria

It is now generally accepted that the manifestations of the nephrotic syndrome result from a primary defect of the renal glomerulus that allows large quantities of protein to pass into the urine. The development of this glomerular lesion may occur during the course of either a primary renal disease or a systemic disease involving the kidney. Prior to the widespread use of the percutaneous renal biopsy the diagnosis of glomerulonephritis was made in almost all adult nephrotic patients with primary renal disease. However, it is well known that many cases of nephrotic syndrome in children lacked the features of classic glomerulonephritis and showed few, if any, glomerular changes. Recent experience in this and other laboratories has indicated that a significant number of adults with the nephrotic syndrome also do not have the characteristic clinical or pathologic findings of proliferative glomerulonephritis, the form of nephritis which is commonly preceded by streptococcal infection. Whether these cases represent a variant of glomerulonephritis or a separate disease entity called lipoid nephrosis, idiopathic nephrosis, or idiopathic nephrotic syndrome (INS) has not been conclusively resolved. We believe that the histologic changes noted in these cases are distinctive enough to support the idea that they represent a separate entity. We refer to this group of cases as idiopathic nephrotic syndrome (INS).

Confusion has arisen in the literature concerning INS because earlier histologic studies have not allowed a clear separation of this entity from proliferative glomerulonephritis. Bell, who was the first to recognize the presence of glomerular changes in INS, introduced the term membranous glomerulonephritis. Although this name has been widely used, it implies a pathogenetic relationship to proliferative glomerulonephritis which has not been proved. Ellis designated as Type 2 nephritis those cases in which the nephrotic syndrome developed insidiously. Unfortunately, this group includes cases of proliferative glomerulonephritis, INS, and perhaps other diseases associated with the nephrotic syndrome.

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With the use of specialized histologic techniques (thin-section light microscopy, phase microscopy, and especially electron microscopy) in the study of renal biopsy material it has become possible to define the glomerular changes with greater precision and to establish definite pathologic criteria for the diagnosis of INS.

Adequate descriptions of normal and abnormal glomerular morphology as determined by electron microscopy are available.[1-4] To recapitulate briefly, the glomerular tuft consists of the capillary loops and the intercapillary tissue or mesangium. The capillary wall is formed by the basement membrane, which is composed of mucopolysaccharides and a scleroprotein, probably a form of collagen. The basement membrane is lined on its luminal side by flattened endothelial cells, whose nuclei may often be seen projecting into the capillary lumen. Minute perforations may be discerned in the endothelial cell lining. Visceral epithelial cells (podocytes) are attached by slender projections to the surface of the basement membrane facing the urinary space. These projections are called foot processes. The basement membrane is the only continuous barrier separating the capillary lumen and the urinary space. The mesangium consists of cells (mesangial cells) and an intercellular substance (mesangial matrix) lying outside of the capillary lumina. The mesangium arises at the glomerular hilus and propagates between the capillary loops into the individual glomerular lobules. It represents a special form of connective tissue with a chemical composition similar to that of the basement membrane, although differing in structure and in response to injury.

The basic morphologic distinction between glomerulonephritis and INS may be expressed as follows: Glomerulonephritis is an "inflammatory" process primarily involving the mesangium and to a lesser degree the capillary walls of the glomerulus. INS is a "degenerative" process which involves the capillary walls but affects the mesangium little or not at all.

The inflammation of glomerulonephritis is manifested by a striking proliferation of the mesangial cells and by a variable exudation of blood elements, particularly polymorphonuclear leukocytes. The

proliferating mesangial cells extend into the capillary wall between the endothelium and the basement membrane. The basement membrane, if involved at all, shows focal variations in thickness and density. Various electron-dense proteinaceous deposits in the capillary wall and the mesangium accompany the inflammatory reaction and may represent antigen-antibody complexes.[19] If the inflammation does not resolve, increasing amounts of mesangial matrix appear in the mesangium and in the capillary wall, eventually leading to sclerosis and obliteration of the capillaries. If severe proteinuria or a nephrotic syndrome accompanies glomerulonephritis (nephrotic glomerulonephritis), the foot processes of the epithelial cells become extensively fused.

The degenerative changes of INS occur in two forms. In the first form the epithelial foot processes are fused and the basement membrane is either normal or only slightly altered.[11] This type of change in the capillary wall has been given the name of foot process nephrosis (FPN). In the second form of INS, called membranous nephrosis (MN), foot process fusion also occurs, but the most striking changes are found in the basement membrane. These consist of irregular projections and electron-dense deposits along the epithelial border. As the lesion advances, the basement membrane progressively thickens, often leading to loss of filtration, constriction of capillaries, and glomerular obsolescence. The relationship between the two forms of INS is uncertain, but they seem to represent separate entities. Although early stages of membranous nephrosis cannot be separated from foot process nephrosis by light microscopy, they can be easily distinguished by electron microscopy.

Despite the obvious histologic differences between nephrotic glomerulonephritis and INS, clinical differentiation is not so clear cut. The clinical and laboratory findings of the nephrotic syndrome—edema, proteinuria, hypoalbuminemia, and hypercholesterolemia—are comparable in both groups. Microscopic hematuria also occurs in both conditions. Although hypertension, modest azotemia, and an elevated serum creatinine are more common in nephrotic glomerulonephritis, they may also be found in INS. There are no laboratory findings that will help differentiate foot process nephrosis from membranous nephrosis.

The prognosis and response to glucocorticoid steroid therapy of these nephrotic states do differ, however. Foot process nephrosis has the most favorable outlook and responds dramatically to steroid therapy. The prospects for recovery from foot process nephrosis treated with modest doses of steroids seem to be excellent. The prognosis for membranous nephrosis does not appear to be as favorable. The effectiveness of steroid therapy is inversely proportional to the severity of membranous change. With minimal involvement, the loss of protein in the urine can be decreased and edema abolished, but with severe changes little improvement can be anticipated. It is not known whether the anatomic process can be halted. We are currently evaluating the response of a number of cases of membranous nephrosis to prolonged courses of moderate and large doses of steroid therapy. Nephrotic glomerulonephritis carries the worst prognosis. Except in a few cases, steroid therapy in moderate and large doses, has not slackened the relentless downhill course of this entity, and in several cases treated by us has apparently hastened the disease process.

The difference in prognosis and response to steroid therapy demand that a definitive diagnosis be made in any adult with the nephrotic syndrome. Since the diagnosis can be established with certainty only on the basis of histologic changes, renal biopsy has become the most important diagnostic test in these patients. With the aid of the refined histologic techniques currently available, it is likely that further study of renal biopsy material will provide information on the natural course of these disease states, give some clues to the pathogenesis of the distinct glomerular lesions, and help determine the response of each form of nephrotic syndrome to different modes of therapy.

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Effect of angiotensin and beta-adrenergic stimulation on venous smooth muscle*

Although the effects of beta-adrenergic agents and angiotensin on the arterial system have been studied extensively, there is considerably less information about the response of veins to isoproterenol or angiotensin. It has been suggested, on the basis of large animal experiments, that activation of venous beta receptors by isoproterenol results in venoconstriction,[1] whereas angiotensin has been considered to have no effect on veins. Our experience with isolated vascular strips suggests that both of the above-mentioned conclusions require some modification. We wish to summarize here the results of some experiments designed to determine the effects of angiotensin and isoproterenol on helically cut venous strips suspended longitudinally on an isotonic lever. Details of the preparation and recording methods in our laboratory have been published previously.[2] In addition, in 4 dogs, a small mesenteric artery and vein were cannulated with a fine polyethylene catheter (I.D. 0.023, O.D. 0.038 inch) at a distance of 1 to 4 cm. from the intestinal border. Direct writer recordings of pressures from these sites and the femoral artery and vein were obtained via Statham P23Db transducers. Injections of 0.85 per cent NaCl control, and of angiotensin amide were made into the mesenteric vein adjacent to the one cannulated, both of these being tributaries of the same vein. The volume of injected solutions was 0.6 ml. delivered over 3 minutes.

Angiotensin produced a small but definite constriction of strips from seven common mesenteric veins, two portal veins, five small mesenteric veins (diameter 1.0 to 2.0 mm.), one gastroduodenal vein, seven lobar pulmonary veins, and one saphenous vein (Fig. 1). The effective concentration of angiotensin (0.005 μg per milliliter) was the same as required for similar preparations of arterial smooth muscle; however, tachyphylaxis was marked and frequently observed. Angiotensin exhibited no effect on eight strips from femoral veins, seven strips from the superior vena cava, one strip from the inferior vena cava, and 4 strips from the saphenous veins. The reactivity of these strips was confirmed by the constrictor effect of norepinephrine.

Preinjection pressures in the mesenteric veins were 4.5, 7.2, 14.0, and 21.0 mm. Hg. Infusion of angiotensin, 1.2 μg per 3 minutes, into small mesenteric veins of 4 dogs produced a rise of 4.1 mm. Hg ±1.2 S.E. in mesenteric venous pressure, without any change in systemic arterial pressure. In one instance this was accompanied by petechiae and a markedly dusky loop of bowel. Control injections of saline had no effect upon mesenteric venous pressure.

The effect of isoproterenol was determined on seven mesenteric, four hepatic, nine lobar pulmonary, seven vena caval, two renal, and seven saphenous vein preparations under spontaneous tone or preconstricted with serotonin (0.1-0.2 μg per milliliter), histamine (1.0-4.0 μg base per milliliter), norepinephrine (0.1-1.0 μg per milliliter). The response of all the veins investigated fell into the same general pattern. Isoproterenol in concentrations of 0.2 to 4.0 μg per milliliter showed marked vasodilator activity. This dilatation could be completely blocked by the β-adrenergic blocker Nethalide (Fig. 2). Higher concentrations of isoproterenol (≥ 5.0-10.0 μg per milliliter) produced venoconstriction, with the transition from vasodilator to vasoconstrictor concentration showing some individual variations. The venoconstrictor effect was abolished by pretreatment[4] with the α-adrenergic blocking agent Dibenamine. Dibenamine did not inhibit the venodilation produced by isoproterenol and the venoconstriction was not blocked by Nethalide. Nethalide (10 μg per milliliter) by itself exhibited a slight venoconstrictor activity. Occasionally isoproterenol showed a diphasic effect, with brief venodilation followed by venoconstriction.

These results extend to veins the general conclusion of recent years that the smooth muscle of different vascular beds is pharmacologically heterogeneous.[5-9] Certainly the responsiveness of splanchnic veins to angiotensin contrasts with the absence of vasomotor response in the majority of canine somatic veins studied by us, in which lack of response to angiotensin is similar to that of hu-

*A preliminary report has been published in abstract form in Circ. Res. 12:193, 1964.

Fig. 1 Venoconstrictor effects of angiotensin on canine pulmonary, hepatic, and mesenteric veins. Base-line irregularities are due to spontaneous contractile activity. *a-c* Angiotensin 0.005 µg per milliliter added at arrow is shown to produce vasoconstriction. *d, e, f* A 100-fold increase in angiotensin concentration (*first arrow*) produces only a slight increase in contractile response. Further addition of angiotensin (*second arrow*) is accompanied by tachyphylaxis, particularly apparent in the mesenteric vein. Contractile responses of same preparations to histamine base 1.0 µg per milliliter in millimeters of lever excursion were pulmonary vein, 39; hepatic vein, 13; and mesenteric vein, 39. Isotonic lever arm ratio was 5:1.

Fig. 2 Alpha and beta-adrenergic responses of canine lateral saphenous vein. Canine lateral saphenous vein brought to initial state of tone by serotonin, 0.15 µg per milliliter. Isoproterenol, 0.2 and 5.0 µg per milliliter relaxes the preparation and 10 µg per milliliter contracts it. *b* Same preparation, during β-adrenergic blockade with Nethalide. The sudden marked vasodilator effect of isoproterenol is now absent. 0.2 µg per milliliter has no effect, and the response to 5 µg per milliliter is vasoconstriction. Same preparation, after α-adrenergic blockade with Dibenamine. The vasodilator effect of isoproterenol is maintained and vasoconstrictor activity is abolished.

man forearm veins.[16] The contraction elicited by angiotensin even in splanchnic veins was generally small, as compared to the response of venous strips to *l*-epinephrine or histamine. This relative lack of sensitivity, however, was not due to higher angiotensin thresholds since effective concentrations of angiotensin were not greater than those required by arterial muscle. Although we observed marked tachyphylaxis to angiotensin, this alone is unlikely to be responsible for the small response which occurred even with high initial doses of angiotensin. It is possible that the magnitude of response is an indication of the proportion of angiotensin-sensitive cells within a pharmacologically heterogeneous cell population. The in vivo mesenteric vasoconstriction produced by local intravenous injection of angiotensin indicates that this effect is not limited to in vitro preparations. The difficulty experienced by previous workers[8] in demonstrating a consistent effect of intra-arterial angiotensin upon mesenteric veins may have been due to an overwhelming arteriolar constriction and a resultant drop in blood flow.

The results obtained with isoproterenol indicat

unequivocally the venodilator role of β-adrenergic receptors. This is further substantiated by the ability of a β-adrenergic blocking agent[14] Nethalide to abolish the venodilator response. Blockade of α-adrenergic receptors with Dibenamine did not prevent the venodilation produced by isoproterenol, but abolished the venoconstriction produced by high concentrations of the latter. A similar vasoconstrictor response to high concentrations of isoproterenol is also exhibited by arterial smooth muscle. This behavior is that expected of an agent with strong β-adrenergic and relatively limited α-adrenergic effects. The relaxing effect elicited by the activation of β-adrenergic receptors of venous smooth muscle was, in the present study, analogous to the behavior of smooth muscle in arteries and splenic capsule.[15] The use of an intact dog-cardiac bypass preparation by previous workers led them to suggest that activation of β-adrenergic receptors leads to venoconstriction. The possibility of this occurring in some portion of the venous bed not sampled in the present study cannot be excluded, but our results obtained with isolated venous smooth muscle fail to provide any evidence for activation of beta receptors initiating contraction of venous smooth muscle.

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Hypophysectomy and heart size

The work of Beznak[1] on the hormonal control of cardiac size and performance has indicated that hypophysectomy profoundly alters hemodynamics and cardiovascular responses in the rat. Extirpation of the pituitary causes a rapid and progressive diminution in the size of the heart which is proportionately greater than the concomitant loss of body weight. This has been attributed to an adaptation of the heart to lower demands (i.e., lowered venous return, decreased cardiac output, and hypotension) resulting from reduced metabolism in the

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hypophysectomized animal. Administration of thyroid-stimulating hormone or thyroxine by keeping metabolism at the normal level, prevents the hemodynamic alterations and consequently inhibits the cardiac atrophy.

Hypophysectomy also prevents the development of cardiac hypertrophy when an increased demand or load is imposed on the heart by aortic constriction or infusion of polyvinylpyrrolidone. The total ability of the heart to respond to an increased demand by hypertrophy is restored by treatment with growth hormone and thyroxine but not by growth hormone or thyroxine alone.

The recent necropsy files of this institution contain the records of 4 women with widespread mammary cancer who had undergone hypophysectomy prior to death. Three of these patients although not emaciated had small hearts (less than 240 grams). Their heart weights varied inversely with the length of postoperative survival. The fourth woman had a normal-sized heart but the hypophysectomy was technically incomplete, 90 per cent of the gland remaining in the pituitary fossa. This case might be regarded as a "sham operated control." Among 35 nonhypophysectomized patients with breast cancer there were only 5 in whom the heart weight was below 250 grams. Four of these however were markedly cachectic, and in the other the adenohypophysis was totally destroyed by metastatic carcinoma.

Hemodynamic studies in man by Bojs and coworkers revealed decreased cardiac output and oxygen consumption in all cases after hypophysectomy. It is possible that similar physiologic mechanisms, promoting cardiac atrophy and preventing cardiac hypertrophy, may be operative in hypophysectomized human beings as well as in rats. Additional clinical and pathologic investigations are needed to confirm this observation.

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Electrocardiographic limb leads: Suggestion for their logical display

The discovery and application of diagnostic techniques has not always developed in an orderly fashion. Thus the optimal application of new information may be interfered with when such information is employed as it is acquired rather than through subsequent thoughtful rearrangement. The purpose of this paper is to propose a logical, rather than historical, order for the display of limb leads of the electrocardiogram based on the progression sequence of axes comparable to the present accepted method of displaying the chest leads.

When the electrocardiogram became available for clinical use early in the century, the classic three leads of Einthoven were employed and remained, for practical purposes, a standard method of displaying the electrocardiographic information. In the nineteen-thirties,* new techniques using unipolar electrodes were introduced. Thus brought in two different concepts in diagnostic method, namely, the exploring electrode and the ability to record electrocardiograms in planes other than the frontal. However, by historical growth, the newly developed unipolar limb leads of the electrocardiogram were added to the old in a fashion which resulted in a nonsequential mounting arrangement (I, II, III, aVR, aVL, and aVF). In contrast, there is a logical

sequential progression in the precordial leads (V_1, V_2, V_3, V_4, V_5, and V_6). It would be inconceivable to accept a disarrangement of the chest leads, e.g., V_1, V_6, V_2, V_5, etc., comparable to the arrangement we now readily accept in the limb leads.

Graettinger and associates recommended a rearrangement of the extremity leads, utilizing both a reciprocal form of aVR and an increase in sensitivity of the unipolar limb leads which presented the leads sequentially.

We are proposing that the theoretic advantages inherent in Graettinger's suggestions can be translated into clinical practice with ease and simplicity by eliminating the necessity for any special lead or modifications. Specifically, our proposal is that we employ only the limb leads currently in use, but that they be displaced in the following order: aVR, aVL, I, II, aVF, and III.

In our experience this sequence is displayed best by vertical mounting (Fig. 1). When so arranged, several advantages may be realized: (1) grouping of related electrocardiographic patterns, (2) ease in identification of electrical position, (3) simplification of material to be committed to memory,

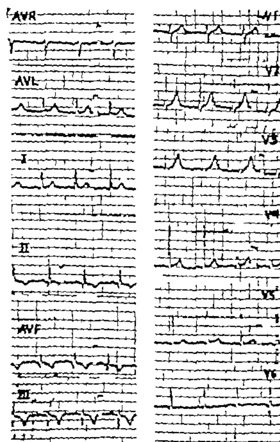


Fig. 1. Electrocardiogram of inferior myocardial infarction. Note that the characteristic Q and T wave abnormalities are grouped together in Leads II, aVF, and III at the bottom of the figure.

(4) aid in the teaching and understanding of vector electrocardiographic relationships, and (5) ease in recognition of misplaced leads.

With the proposed arrangement, related electrocardiographic patterns are sequentially grouped instead of being scattered as in the manner of mounting now employed. For example, the characteristic Q waves of inferior myocardial infarction will be localized and visible together at the bottom of the column in II, aVF, and III (Fig. 1).

Electrical position is quickly identifiable by noting the lead containing the largest R wave: right predominance appears in the lead at the bottom, and left predominance in the lead near the top of the illustration.

With the sequence aVR, aVL, I, II, aVF, and III, corresponding deflections of the electrocardiogram will approach a sine wave pattern. For example, the P wave may be negative in aVR, isoelectric in aVL, slightly upright in I, taller in II, smaller in aVF, and flat in III. Accordingly, the initial, mid, and terminal portions of the QRS complex, S-T, and T waves also undergo a sine wave sequence wherein there is increasing magnitude, regression, reversal of polarity with increasing magnitude, regression, etc., as can be seen in the figure.

Since the entire electrocardiogram in this new method of mounting has a progressive sequence, it serves to organize and thus simplify material that must now be committed to memory.

For the student, this method presents a geometrically sound basis for understanding vector electrocardiographic relationships, for he may now visualize the sequential logic of the material rather than learning solely "by rote."

Finally, the arrangement is advantageous in offering a ready opportunity to detect misplaced leads which "break" the sine wave sequence.

A slight inconvenience to the interpreter in comparing the newly mounted tracings with previous electrocardiograms will occur, but this is temporary. From the technical aspect, the selector switch of the machine may be rewired, or one may simply indicate numerically the desired sequence on the selector switch. On the other hand, the revision may be achieved merely by the appropriate mounting of the electrocardiographic leads.

In summary, we propose that the various limb leads of the electrocardiogram which are currently in use be grouped in series as follows: aVR, aVL, I, II, aVF, and III. This achieves an orderly display of the electrocardiographic information, facilitates teaching of the subject in a logical fashion, and provides a rational basis for the accurate interpretation of the records.

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internist or even cardiologist will find the time to read and digest the material provided. The greatest appeal, of course, will be for those individuals with a special interest in the finer points of the disorders of the cardiac mechanisms. For them this book should prove to be quite fruitful.

CONTROVERSY IN INTERNAL MEDICINE. Edited by Franz J. Ingelfinger, M.D., Arnold S. Relman, M.D., and Maxwell Finland, M.D. Philadelphia, 1966, W. B. Saunders Company. 679 pages. Price $14.50.

This is an interesting book on controversial clinical problems in medicine. Most subjects are discussed in a debating and philosophical vein concerning the practicing physician. For example, among the problems debated are these: the policies and activities of the American Board of Internal Medicine, arteriosclerosis and diet, when to use drugs for hypertension, the anticoagulant dilemma, dietary treatment of peptic ulcer, management of gastric ulcer, classification of the cirrhoses, significance and management of asymptomatic bacteriuria, to catheterize or not to catheterize, treatment of emphysema, diagnosis of unilateral renal disease, lies, damn lies and statistics, and others. This is a very good book. It is well written and each problem is presented by authors with somewhat different points of view. Finally, the debate is interpreted by a comment by a "Solomon," who indicates the more rational attitude justified by the state of knowledge and practice of today.

The authors are all well known. In fact, if the reader knows the authors well, he can predict the points of view which he will find in their respective discussions. Some of the authors who are not physicians in active practice discuss problems confronting practicing doctors. Thus, physicians in practice who read the book will find that some discussions reflect a lack of details of experience and information gathered through night-and-day responsibility for patients. This is a very interesting book which is highly recommended for leisurely and thoughtful reading.

CARDIAC EVALUATION IN NORMAL INFANTS. By Robert F. Ziegler, M.D., Henry Ford Hospital, Detroit, Mich. St. Louis, 1965, The C. V. Mosby Company. 170 pages. Price $12.75.

This small book of 170 pages by Ziegler is concerned primarily with one of the most difficult problems in medicine, i.e., the diagnosis of a normal state of health. To know when a heart is absolutely normal is often very difficult because of the marked variations of the normal. The diagnosis of a normal heart is even more difficult in the neonatal period when the circulation is changing postnatally from the fetal to the normal nonfetal type and progressively to the adult type. The importance of an accurate diagnosis of the state of health of the heart becomes even more pressing each year because of the influence of the lay press and its propaganda about heart disease. Parents want to know immediately after birth, "Is the heart normal? Is there a congenital defect?" The pediatrician is constantly asked such questions throughout the patient's childhood.

Ziegler discusses the problems very well and from a practical clinical point of view. He discusses the problems of murmurs in normal hearts as well the differentiation of a large heart from a normal one. The evaluation of cyanosis and pseudocyanosis and the influence of systemic diseases, such as infections, on a previously normal heart are briefly considered. The author has presented some of the important clinical problems encountered in the diagnostic evaluation of the heart in normal infants. The problems clinicians must handle most often are effectively discussed by Dr. Ziegler. The book has good illustrations, although a hand lens would be useful in studying the electrocardiograms; a fairly extensive bibliography is appended to the book. All pediatricians, pediatric cardiologists, and general practitioners will find this book profitable to read.

HYPERTENSION. Volume XIII. Proceedings of the Council for High Blood Pressure Research, American Heart Association, Cleveland, November 13 and 14, 1964. New York, 1965, The American Heart Association, Inc., 210 pages. Price $2.50.

This volume represents the proceedings of the meetings of the Council for High Blood Pressure Research of the American Heart Association held in Cleveland, Nov. 13 and 14, 1964. This series of monographs of the American Heart Association has been very good, and this one upholds the tradition. The monograph presents a series of papers with associated bibliography and interspersed discussions. Although the subjects discussed are not new and those who follow the literature will recognize illustrations and concepts, the volume gathers into one source some interesting papers on hypertension written by active investigators in the field. The book is recommended to students, house staff fellows, and physicians, as well as physiologists and investigators.

ELECTROLYTE AND CARDIOVASCULAR DISEASES. Vol. I. FUNDAMENTAL ASPECTS. Edited by Eors Bajusz, University of Montreal. Baltimore, 1965, Williams & Wilkins Company. 412 pages. Price $16.

This book is primarily a series of summary papers on experimental aspects of electrolyte physiology in cardiovascular disturbances. Volume I is concerned with fundamental aspects of electrolyte metabolism, whereas Volume II is to be concerned with clinical problems. The authors are from all over the world, but Dr. Bajusz has translated all papers into English for the convenience of the reader. As would be expected

much of the material has already been published elsewhere however this volume provides a single source of the material for the reader who may not wish to search the literature for original and previously published paper A good bibliography is appended to each paper Some of the papers are very good and the authors are experienced in investigation in the field of electrolyte metabolism whereas other author are not so expert and the paper not so good The papers on electrolyte and myopathies and vascular smooth muscle are very good and should interest the reader The reader will learn if he does not already know the extent e importance of electrolyte metabolism in health and disease of heart muscle This book is highly recommended

Books received

Ferment in Medicine. By Richard M Magraw M D and Daniel B Magraw M B.A., Philadelphia 1966, W B Saunders Company 272 pages. Price $6 50

Modern Treatment Vol 2 No. 6 November 1965 Treatment of Venous Disorders by John A. Spittell, Jr M D Treatment of Disorders of the Ear Nose and Throat by Walter H Maloney M D Cumulative Index 1964-1965 New York 1965 Hoeber Medical Division of Harper and Row Publishers 1500 pages per year $16 00 per year by subscription (published bimonthly).

Death in the Operating Room. By Antonio Bobe Springfield Ill 1965 Charles C Thomas, 105 pages. Price $5 50

Announcements

The dates of the Tenth Congress of the Pan Pacific Surgical Association are as follows *Part I* Sept 20-28 1966 in Honolulu Hawaii. Second Mobile Educational Seminar—*Part II* September 28-October 10 1966 in Japan and Hong Kong *Part III* September 28-November 1 1966, in Japan Hong Kong The Philippines, Thailand, India Singapore Australia and New Zealand

For further information write Pan-Pacific Surgical Association Room 236 Alexander Young Bldg Honolulu Hawaii, 96813

A Symposium on Cardiovascular Disease will be presented by the Department of Radiology of the University of Kentucky Medical Center from May 2 to May 6 1966 immediately preceding the Kentucky Derby Besides staff members of the University of Kentucky a number of outstanding guest faculty will be attending

Inquiries concerning this Symposium should be addressed to Dr Nicholas J Pisacano, Director of Continuing Medical Education University of Kentucky Medical Center Lexington Ky 40506.

The Annual Meeting of the Ballistocardiograph Research Society will be held in Haddon Hall Atlantic City N J., on April 30 1966

For information contact Secretary Dr Abraham Noordergraaf Department of Biomedical Engineering Moore School of Electrical Engineering University of Pennsylvania Philadelphia, Pa., 19104

Obituary

Professor A. L. Myasnikov

On Nov 14 1965 at the height of his outstanding academic and research career Professor A. L. Myasnikov suddenly died

Professor Myasnikov was one of the most distinguished cardiologists in the world He was an outstanding member of the Academy of Medical Sciences in Russia and was an active member of the Board of Editors of the AMERICAN HEART JOURNAL at the time of his death

Professor Myasnikov was born in 1898 He received the doctor of medicine degree in 1922 and worked as the assistant of Professor Lung in the First Medical School in Leningrad At the age of 33 he became head of the Department of Internal Medicine in Novosibirsk and then became Chairman of the Department of Internal Medicine in the Third Medical School in Leningrad in the Military Navy Medical Academy In 1948 he became Director of the Institute of Therapy of the Academy of Medical Sciences of the USSR, working concurrently as Chief of Clinical Therapy at the First Moscow Medical School

Professor Myasnikov s scientific interests and achievements were many Besides cardiology his studies included the pathology of the liver the field of hematology and infectious diseases and he wrote extremely useful handbooks for medical students and physicians in the USSR. The last ten years of his life were devoted primarily to problems in cardiology hypertension arteriosclerosis and coronary insufficiency He was very active as an international medical statesman in the field of cardiology and medicine In recognition of his world wide interest in cardiology he was awarded the Gold Stethoscope in 1964 Professor Myasnikov was the author of 9 monographs 4 handbooks and over 200 scientific papers He was editor in-chief of the *Journal of Cardiologia* of the USSR and was a member of the editorial boards of five foreign journals including the AMERICAN HEART JOURNAL.

Professor Myasnikov was also a member of the Presidium of the International Therapeutic Society the International Society of Cardiologists and an honorary



A. L. Myasnikov 1898-1965

member of the Romanian Academy of Sciences and of the Serbian Academy of Sciences and Arts. He was awarded the 'Order of Lenin and The Order of the Banner for his work in his country

Professor Myasnikov was a very fine person and an outstanding scientist and teacher He was a man of great charm and had friends throughout the world Those who knew him appreciated his personal qualities and his sincere humanitarianism as well as his outstanding accomplishments as a physician

His death is a great loss to world medicine and cardiology

American Heart Journal

May 1966 Volume 71 Number 5

Editorial

Energy, recreations, and the cardiac patient

R. Passmore, M.D.
Edinburgh, Scotland

To a medical student before the discovery of chemotherapy and antibiotics, rheumatic fever and bacterial endocarditis were familiar diseases to be seen in every general medical ward. Physicians then emphasized, very properly, the important role of rest in the treatment of these inflammatory conditions. Nowadays, ischemic heart disease has become by far the most important cause of cardiac disability. Is rest beneficial for this condition? It is established that, in athletes, exercise causes hypertrophy of the heart and also that athletes live at least as long as other people. Presumably the vessels of the coronary circulation also hypertrophy as a result of the athlete's training program. Might not exercise also benefit the coronary circulation when it has been impaired by degenerative disease? If so, how much exercise should be prescribed?

The maximum level at which fit young men can work requires the utilization of oxygen at rates between 3.5 and 4 liters per minute. This is known as the *maximum oxygen capacity*.[1] It is about sixteen times the utilization of oxygen at rest. Trained athletes may have a slightly higher value. Exercise at this level is associated with the accumulation of a large oxygen debt, acidemia due to the buildup of the concentration of lactic acid in the blood, a rising pulse rate and body temperature, and the rapid onset of fatigue which soon limits the exercise. If exercise is carried out at about half this rate, none of these things are observed. The work may then be said to be within the subject's *aerobic capacity*. For instance, if the writer, who is 55 years old, walks at 4 m.p.h. on a treadmill, he uses oxygen at the rate of 1.1 liters per minute and his pulse rate is steady at about 120. After an initial rise of about 1°C, body temperature remains steady. Walking can be continued at this rate for 10 miles. When he stops walking, the pulse returns to the resting level within 5 minutes, the oxygen debt is less than 1 liter, the lactic acid in the blood is within normal limits, and there is no fatigue. However, if he tries to walk at 5 m.p.h., using oxygen at the rate of about 1.5 liters per minute, the pulse rate continues to rise slowly, fatigue sets in, and he would have difficulty in continuing after about half an hour. This subject's aerobic capacity is work which involves the utilization of oxygen at the rate of a little over 1.1 liters per minute.

Common sense and experience both indicate that it is unwise for a patient with a cardiac disability to exercise so as to cause early fatigue (i.e., up to maximum oxygen capacity). However, there would

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seem to be no reason why such a patient should not work up to the limit of his aerobic capacity even though this may be lowered by a limited power of the circulation to transport oxygen to the working muscles Such exercise might be beneficial[2] The aerobic capacity of a subject is not difficult to measure with proper equipment. Several parameters could provide a suitable index. The level of work at which the pulse rate remains steady may be the simplest. Nowadays no self-respecting physiologist would begin to study the responses of the healthy human body to exercise without a power-driven treadmill with which the exercise can be accurately graded In many hospitals the exercise tolerance of cardiac patients is still assessed by tests which belong to the prescientific age. It could be determined much more precisely[3]

What sort of exercises are likely to be within the aerobic capacity of patients? Walking is an activity with which all are familiar It can be readily graded to suit a patient's capacity The energy required is directly related to speed and to the weight of the subject and is the same for both sexes. Table I sets out the energy cost of walking on the basis of many laboratory measurements. For any individual a prediction using the table is likely to be accurate within ± 15 per cent Walking up a moderate hill (gradient 1 in 20) will increase the expenditure of energy by about 30 per cent On a steep hill (1 in 10) it will nearly be doubled The figures are given in calories, which allow comparison with the intake of energy in food (One gram of carbohydrate will suffice for a 140-pound man to walk at 3.0 m p h for 1 minute.) Estimates of the expenditure of energy in man are based on measurements of oxygen consumption (indirect calorimetry) For rough calculations 1 liter of oxygen used may be taken as equivalent to 5 kilocalories of energy A recent monograph[4] describes modern techniques for indirect calorimetry including those suitable for use in field conditions.

The table can be used by physicians who wish to prescribe a regimen of physical exercise and allows both the total amount of energy and the rate of expenditure of energy to be assessed Walking at 4 m p.h is within the aerobic capacity of healthy middle-aged men Women with their shorter legs are at a mechanical disadvantage and many find that a speed above 3½ m p.h is uncomfortable The increased weight of obese subjects imposes a handicap and many could not walk at this speed until they have reduced Physiologic considerations suggest that walking may be prescribed with safety for a patient with cardiac disabilities at a rate up to the limit of his aerobic capacity provided that this does not cause anginal pain A man weighing 160 pounds who is advised to walk for two periods of 30 minutes each a day at 2.5 m p.h will expend about 230 kilocalories in the exercise and his circulatory system must be able to supply oxygen to the muscles continuously at a rate of about 760 ml per minute.

There are many recreations which provide suitable light exercise Industrial work has been classified[4] as light if it requires an expenditure of energy between 2.5 and 5.0 kilocalories per minute as moder

Table I Expenditure of energy in kilocalories per minute related to speed and gross body weight[4]

Speed (m p.h.)	Weight (lbs.)						
	80	100	120	140	160	180	200
2.0	1.9	2.2	2.6	2.9	3.2	3.5	3.8
2.5	2.3	2.7	3.1	3.5	3.8	4.2	4.5
3.0	2.7	3.1	3.6	4.0	4.4	4.8	5.3
3.5	3.1	3.6	4.2	4.6	5.0	5.4	6.1
4.0	3.5	4.1	4.7	5.2	5.8	6.4	7.0

ate if between 5.0 and 7.5 kilocalories per minute and as "heavy" if over 7.5 kilocalories per minute. Recreations can be similarly classified. The energy expended by subjects when engaged in a number of pastimes and recreations has been measured and reviews are available.[4,7] The following activities may be graded as "light" (between 2.5 and 5.0 kilocalories per minute): archery, dancing, golf, billiards, fishing, swimming, bowls, gardening, table tennis, croquet. Each may provide beneficial and enjoyable exercise for partially incapacitated persons. However, warning is necessary. Many of these recreations can involve "heavy" exercise. Thus, if a person goes to a dance and takes the floor for an eightsome reel or other country dance, the exercise will be heavy and the rate will be up to 8 kilocalories per minute or more, but if he restricts himself to ballroom dancing, he need not exceed a rate of 5 kilocalories per minute. Gardening can also be "heavy" work. Digging is inevitably so. The use of power-driven cultivators, hedge-cutters, and motor mowers will reduce the time taken to do a job but these are heavy machines and their use may entail "heavy" work. Weeding, hoeing, pruning, and bedding out can all be made "light" provided that the gardener is prepared to work slowly. Golf is usually "light" exercise, but not on a hilly course or in strong winds or for some incompetent performers. An Olympic swimming champion will almost certainly have a heart capable of supplying his muscles with 4 L. of oxygen or more each minute, but one can swim slowly and leisurely, exercising all of the muscles of the body and relieved of most of the effort required to support its weight.

The list, which must be by no means complete, does, however, give a choice of active recreations, which may be recommended to middle-aged and elderly people with or without a cardiac weakness—provided that always they use moderation. More facilities for these recreations are needed and also education. It is not only young athletes who require the help of coaches.

Americans are gluttons for sedentary work. At a recent medical conference in New York during January, a visitor could not but wonder that the lecture hall was packed with people from 9 A.M. to 6 P.M. for 6 days of the week, yet when walking in snow-covered Central Park before breakfast, he was as lonely as on a Scottish moor. The Park is beautiful . . . but this sermon must cease. There is time for a half hour of practice on the golf course before the light fades.

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Clinical communications

The electrocardiographic "intermediate phase" of an acute myocardial infarction

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Herman H Shapiro M.D
Madison Wis

The immediate and evolutionary electrocardiographic changes of an acute myocardial infarction are well known. One of us (H.H.S.) has noted the interruption of the usual progressive electrocardiographic changes of an acute myocardial infarction by an unexpected improvement in T wave configuration or even a return to normal of the entire QRS-T complex, with subsequent resumption of the evolutionary changes of the acute infarction on serial tracings. We have referred to this phenomenon as the intermediate phase of an acute myocardial infarction. Patients presenting with this electrocardiographic phenomenon may be prematurely advised of their apparent well being with potentially dire results.

The purpose of this paper is to illustrate 7 such instances. Although it is assumed that this is a familiar electrocardiographic occurrence, it has not been critically documented in the available literature.

Material

The 7 representative patients presenting with the intermediate phase were observed at the University Hospitals, Madison Wisconsin. All presented with clinical symptomatology suggesting acute coronary insufficiency or myocardial infarction. Five were males, with an over-all age range of 41 to 71 years. The clinical highlights of the individual patients will be presented initially.

Case reports

Case 1 R.F.K., a 53-year-old man, was admitted to University Hospitals with substernal pain radiating to both shoulders and upper arms. The pain had begun the preceding day, had abated overnight but had returned on the day of admission with an accompanying cold sweat and shortness of breath. *He alluded to a similar but milder episode of chest pain 5 years earlier.*

Physical examination revealed a slightly obese, apprehensive and dyspneic man. His admission electrocardiogram of Dec 31 1958 (Fig 1), revealed focal T-wave inversion in Leads V and V_4, with T-wave flattening in Lead V, suggesting an acute anteroseptal ischemic episode. The progress tracing of Jan. 6 1959 revealed marked improvement. Although there was no recurrence of chest pain the progress *tracing of Jan 13 1959* suggested evolution to an acute anteroseptal myocardial infarction, which was confirmed on the serial tracings of Jan. 16 1959 and Feb. 12 1959. He subsequently had an uneventful hospital course and was discharged on Feb. 20 1959.

Case 2 M.H., a 50-year-old man, was admitted to the hospital for evaluation and treatment of radiating substernal pain noted 3 days earlier. He related a 2 year history of angina pectoris brought on by exertion. His initial electrocardiogram of July 7 1960 (Fig 2), revealed isolated T-wave inversion in Lead V_1 associated with marked counterclockwise rotation. One day later elevated S-T segments and marked T-wave inversion were noted across the entire anterior wall, suggesting an acute anterior myocardial ischemic episode. The progress

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tracing 5 days later, however, revealed resolution of the S-T segment and T-wave changes. Without recurrence of pain, subsequent electrocardiograms revealed apparent loss of the septal R wave in Lead V and isolated T wave inversion in Leads V and V_4, which progressed to a massive anteroseptal myocardial infarction by Aug. 8, 1960. Recovery was uneventful and he was discharged from the hospital on Aug. 9, 1960.

Case 3. M. O., a 44-year-old woman, was admitted to the hospital for evaluation of migraine headaches and radiating substernal pain, the latter of 2 days duration. She had been receiving Cafergot for control of the vascular headaches. Her admission and progress electrocardiograms of Sept. 22 and Sept. 23, 1952 (Fig. 3), revealed an acute anterior myocardial infarction. Marked improvement was noted on the progress *tracing of Sept. 26, 1952*, with only minimal T-wave inversion seen in Lead V_4. Subsequently, marked symmetrical T-wave inversion was seen across the entire anterior wall, which remained stable over a 1-month period. She was discharged on Nov. 8, 1952.

Case 4. A.W., a 61-year-old man, was admitted to the hospital for evaluation of radiating substernal

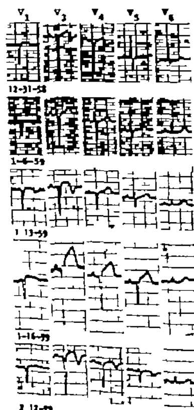


Fig. 1. Case 1. Serial electrocardiogram showing acute anteroseptal myocardial infarction. The intermediate phase is seen on Jan. 16, 1959.

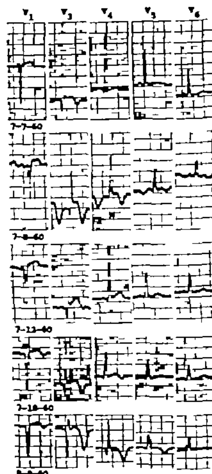


Fig. 2. Case 2. Serial electrocardiograms showing acute anteroseptal myocardial infarction. The intermediate phase is seen on July 12, 1960.

pain of 2 day duration. He related a 2-month history of similar pain associated with effort or meals. His admission electrocardiogram of Sept. 29, 1963 (Fig. 4) revealed small initial Q waves in Leads V, V, and V, with progression to acute anteroseptal myocardial infarction on the tracing 1 day later. Although marked improvement was noted in T wave configuration on the tracing of Oct. 4, 1963, subsequent tracings revealed recurrence of the symmetrically inverted T waves in Leads V and V_4. He was discharged from the hospital on Nov. 9, 1963. The follow-up tracing of Dec. 6, 1963, revealed a residual anteroseptal myocardial infarction.

Case 5. R. E. C., a 1 year-old man, was admitted to the hospital on Feb. 26, 1963, for evaluation of substernal pain of 3 days duration. His admission electrocardiogram of Feb. 27, 1963 (Fig. 5) revealed an acute anterior myocardial infarction. Marked improvement in T-wave configuration was noted on the tracing of March 5, 1963, with recurrent T-wave inversion on the serial tracing of March 13, 1963.

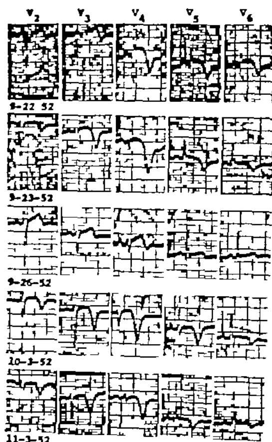


Fig. 3. Case 3. Serial electrocardiograms showing acute anterior myocardial infarction. The intermediate phase is seen on Sept. 26, 1952.

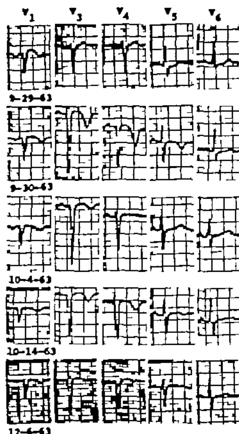


Fig. 4. Case 4. Serial electrocardiograms showing acute anteroseptal myocardial infarction. The intermediate phase is seen on Oct. 4, 1963.

He died on March 28, 1963. *Postmortem examination revealed a massive acute anteroseptal myocardial infarction.*

Case 6. A.Z., 51-year-old man, was admitted to the hospital because of an acute episode of chest pain. There was a 3-week history of angina pectoris. His admission electrocardiogram of July 10, 1958 (Fig. 6) revealed symmetrical T wave inversion in Leads V-V6. A progress tracing on July 14, 1958, showed upright T waves. On the evening of July 17, 1958, he had recurrent chest pain and an electrocardiogram taken the following morning disclosed T-wave inversion identical to that seen on admission. The remainder of his hospital course was uneventful and he was discharged on Aug. 12, 1958. An electrocardiogram taken on Aug. 19, 1958, showed persistent T wave changes, suggesting a stable anteroseptal infarction.

Case 7. M.M., a 41-year-old woman, was admitted to the hospital because of an acute episode of anginal chest pain. She gave a history of chest pain intermittently for 8 months. Bilateral oophorectomy had been performed 9 years previously. Her initial electrocardiogram, taken on April 1, 1965 (Fig. 7), revealed T-wave inversion in Leads V-V6. An electrocardiogram taken on April 5, 1965, was

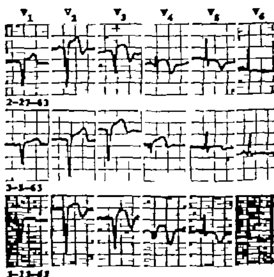


Fig. 5. Case 5. Serial electrocardiograms showing acute anterior myocardial infarction. The intermediate phase is seen on March 5, 1963.

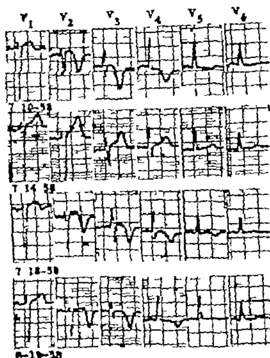


Fig. 4 Case 6 Serial electrocardiograms showing acute anteroseptal myocardial infarction. The intermediate phase is seen on July 14 1958.

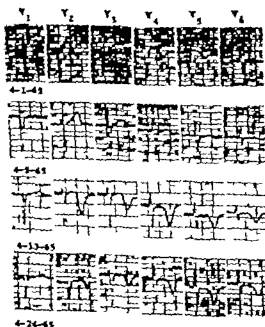


Fig. 7 Case 7 Serial electrocardiograms showing acute anterior myocardial infarction. The intermediate phase is seen on April 5 1965.

normal. Chest pain recurred 8 days after admission and continued intermittently during hospitalization. On April 13 1965, a progress tracing was obtained and it again showed T wave inversion in Leads V_1-V_4. These changes persisted on a tracing taken on April 21 1965 and are consistent with an anterior myocardial infarction.

Discussion

The electrocardiographic survey of these 7 patients illustrates what we have chosen to call the "intermediate phase" of an acute myocardial infarction. This phase may be seen as a temporary interruption in the classic evolution of the infarction pattern with either marked improvement in S-T segment or T wave configuration or of the entire QRS-T complex. Serial tracings, taken at an opportune time, are necessary to document this transient phenomenon.

Although the mechanism for this apparent electrocardiographic improvement is not clear several possible explanations present themselves (1) There may be temporary reversibility of the acute myocardial ischemic changes enhanced by adequacy of collateral coronary circulation enforced bed rest administration of oxygen, and control of existing cardiac arrhythmias with subsequent recurrence of an episode of acute myocardial ischemia or infarction (2) Potassium may be liberated from the ischemic myocardial cells with a temporary increase in the extracellular potassium concentration resulting in a transient increase in T wave amplitude. Experimentally it has been shown that the injection of potassium salts into the subepicardium results in gross S-T segment elevation and T wave peaking in overlying leads.[8] (3) The intermediate phase itself may conceivably represent an acute episode of myocardial injury or ischemia, resulting in S-T segment elevation and upright T waves, erroneously suggesting improvement. (4) There may be faulty precordial electrode placement

The exact incidence of the "intermediate phase" associated with acute myocardial infarction is not known but it is probably a frequent, although transient electrocardiographic finding. Serial tracings within the first week of an acute myocardial infarction are most apt to document it.

This entity is usually established by the retrospective review of serial electro-

cardiograms Familiarity with its presentation should allow the clinician to place this transitory electromotive phenomenon in its proper perspective Failure to do so may result in the premature dispatch of the therapeutic regimen In all 7 instances currently reported the myocardial lesions occurred in the anterior wall

Summary

An intermediate phase in the electrocardiographic evolution of an acute myocardial infarction is described This phase is characterized by temporary alteration of the QRS-T complex, suggesting a reversion toward normal or toward a configuration observed earlier in the course of the infarction Failure to recognize the phenomenon may lead the physician to overlook the presence of an actual myocardial infarction The true incidence of this variant of the classic electrocardiographic sequence will undoubtedly become more evident as clinicians become familiar with its presentation.

We are indebted to Dr Richard H Wasserburger for helpful suggestions.

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Viscosity of blood in normal subjects and in patients suffering from coronary occlusion and arterial thrombosis

An in vitro study in the absence of anticoagulants by means of a rotational cone-in-cone trolley viscometer

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*D. G. Julian, M.A., M.D., M.R.C.P.***
*G. E. Miller, B.E., M.B., B.S.****
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Many abnormalities in the characteristics and constituents of the blood have been described in patients with coronary and peripheral arterial disease. These include hypercholesterolemia, hypertriglyceridemia, increased hematocrit, increased platelet stickiness, and increased viscosity.

Dintenfass[1-3] has observed that some patients with venous thrombosis and coronary occlusion have increased blood viscosity at low shear rates, and obtained a highly significant difference between a group of normal subjects and a group of patients, the latter being mainly ambulatory patients. Dintenfass attributed the difference in blood viscosity to an enhanced aggregation of the red cells in thrombotic states.

It was the purpose of the present study to test and to extend these observations to a larger number of normal subjects and to nonambulant patients with cardiovascular diseases. As will be seen, although the results obtained confirm in principle ideas expressed earlier,[3] certain new correlations were found to exist. A new and important observation shows that blood viscosity is not a function of age in the healthy donor. A rather unexpected result of this investigation includes findings on a difference in the clotting times of blood and in the clotting time ratios, obtained at high and low rates of shear, between the normal subjects and the patients.

Experimental method

The development of a cone-in-cone viscometer was necessitated by a requirement for an instrument sensitive enough at very low rates of shear, easy in operation, easy to clean, and simple in principle. This instrument[1-3] has been further modi-

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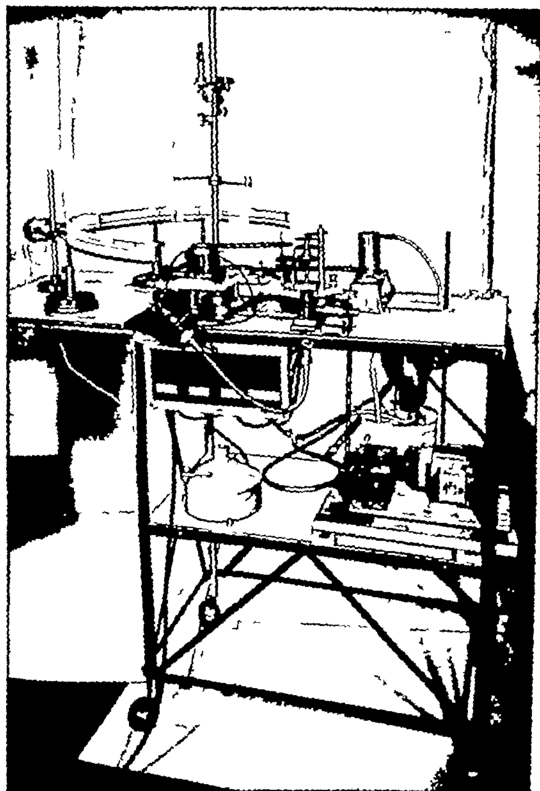


Fig. 1. The cone-in-cone trolley viscometer. The lower level of the trolley accommodates an electric motor, a "Zeromax" stepless drive (*right front*), a thermostat (*right back*), a transformer (*left*), and a panel of switches. The top level of the trolley accommodates the cone-in-cone viscometer (*center*), a spotlight and a semicircular scale (*left*), a reduction gearbox, and the pulley of the driving unit (*right*). A tachometer is visible in front and above the panel of switches.

fied by putting it on a trolley and thus making possible the study of blood viscosity at the patient's bedside.[4]

A view of the trolley viscometer is presented in Fig 1 The viscometer consists of a stand a torsion strip and two coaxial cones enclosed in a thermostated jacket the latter is presented diagrammatically in Fig 2 The internal cone, suspended on a copper beryllium torsion strip is made of Teflon the interior of the cone is hollowed and filled with lead in such a way as to reduce the center of gravity The external rotating cone is made of brass. A gap of 5 degrees exists between the surfaces of the cones, the semiangles of the cones being 35 and 40 degrees against the vertical axis. The torsion strip used in these experiments has a cross section of 0 002 by 0 025 inches and a length of 20

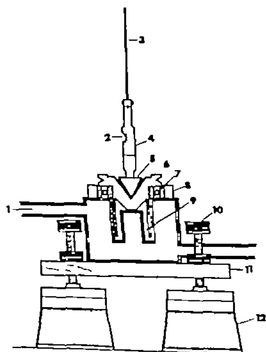


Fig 2 A schematic diagram of the cone-in-cone assembly and of the base of the viscometer 1 Thermostated jacket. 2 A small mirror mounted in the lower suspension holder 3 A torsion strip 4 Lower suspension. 5 The internal cone. 6 The external rotating, cone resting on the ball bearing, 7 and supported by a ring. 8 9 Oil-filled space between the external cone and the thermostated jacket 10 Leveling screws 11 The base of the viscometer (lead ballast is not indicated). 12 Shock absorbers.

cm Adjustments in the position of the torsion strip are carried out by means of two micrometers. The alignment of cones is controlled by means of two spirit levels placed at right angles to each other and by means of a plum bob centering onto a perforated disc placed (for this purpose) in the orifice of the rotating cone.

In order to prevent vibrations, the electric motor (lower level of the trolley) and the viscometer (higher level of the trolley) are mounted on shock absorbers. Additionally the base of the viscometer is weighted down with 10 pounds of lead

The viscometer was calibrated using standard oils obtained from the National Standards Laboratory C.S.I.R.O., Sydney The rates of shear were calculated using an equation of Oka[5] the solution of which was given earlier[2] The coefficient of proportionality between the rate of shear D in reciprocal seconds and the number of revolutions per minute f ($D = kf$) is equal to 0 732 The range of rates of shear is from 0 003 to 118 sec $^{-1}$ the corresponding range of revolutions per minute is from 0 004 to 160

The actual determination of blood viscosity was carried out as follows Samples of blood were obtained by venepuncture using uncoated (untreated) needles and syringes. Usually about 5 ml of blood was taken at one time, of which 1 ml without anticoagulants, was used immediately for study of viscosity whereas the remaining blood was poured into EDTA bottle for subsequent tests of erythrocyte sedimentation rate and hematocrit. A stop watch was started at the moment at which the first drop of blood appeared in the syringe during venepuncture. One milliliter of blood was poured into the gap between the cones, zero position of the lightspot was checked and then the drive was started Deflection of the torsion strip was observed as the movement of a light spot on the semicircular plastic scale The rotational velocity was checked by observing the tachometer

Temperature was kept constant at 37° C It is important to note that the determinations of viscosity were carried out always first at the lowest and then at progressively increasing rates of shear Viscosity of blood was not affected by the clotting

process during the first latent period of about 2 until 4 minutes after venepuncture. Since the test was started within 1 minute after the first drop of blood appeared in the syringe, a period of 1 to 3 minutes was usually available for the determination of viscosity It was necessary to use two or three samples of blood in order to establish the flow curve of blood over the whole range of rates of shear

The time elapsed from the first moment of venepuncture to the moment at which the viscosity of blood starts to increase due to clotting is accepted as the *clotting time* of the sample Observations of the changes in viscosity during clotting were carried out at a constant rate of shear on each sample tested however at least two samples of each blood were tested

Selection of donors This study is based on a new series of donors and does not include donors, or data, described in earlier papers[1,2] Four groups were tested The first group comprised healthy men volunteers who were mainly research fellows residents, and staff of the hospital. The second group consisted of healthy women volunteers who were nurses and female students. The third group consisted of patients suffering from acute or old myocardial infarction This division into acute and old infarctions was quite arbitrary the first 14 days after the attack being considered as the acute phase. Two of these patients were treated for congestive heart failure. The fourth group was composed of patients suffering from arterial thrombosis.*

All patients were nonambulatory (bed ridden) This was exactly the reason that a movable trolley viscometer was constructed

None of the patients was febrile when the test was performed In no case was the patient treated with anticoagulants Two of the patients died after the tests (Table III)

Laboratory data on normal subjects and patients are given in Tables I II III and IV

Rheological nomenclature The "rate of shear" or the velocity gradient" is a function of the relative velocity of the

*Most of these patients were under the care of Dr Alan Sharp, and we wish to acknowledge his permission to study them.

Table I Laboratory data on normal men

Code	*Age (yr)*	*Hematocrit*	*ESR*
N50*	37	44 47 5	1
N51	37	46, 47	4 5
N62	25	47	1 5
N63	27	44	4
N64	25	51 3	1
N65	30	50 3	1
N66	31	42 8	1 2
N70	23	49	1
N71	22	47 5	1 5
N72	22	48 5	1
N75	43	46 3	4 5
N91	35	43 1	10 5
N93	27	43 7	2
N98*	45	45	2
N99	35	43 5	3
N100	22	43 5	2
N114	34	46	14
N115*	28	47	3 5
N116	59	—	—
N117	32	48	1
N118	70	—	—
N121	28	43	1
N122	34	46	14
N124	17	47	4
N125	33	43 5	3
N126	26	47	4
N130	55	—	—
N133	66	43 2	6
N134	55	40 8	24
N135	62	50 8	2
N136	43	44	4
N138	82	38 6	3
N139	63	39	8
N140	73	43 5	43
N141	52	49	0 1

Donor was tested repeatedly

Table II Laboratory data on normal women

Code	*Age (yr)*	*Hematocrit*	*ESR*
N52	24	40 5–41 5	4 5
N53	21	41 5–42 0	7
N54	27	38 5	11
N59*	22	41 4	3
N76	26	43 7–44 4	2 5
N77	24	40 5	—
N79*	19	40 5	7 5
N85*	26	40 5	10 3
N131	17	—	—

Donor was repeatedly tested at an interval of several days (number of tests from 4 to 20).

Table III Laboratory data on patients suffering from myocardial infarction

Code	*Age (yr.)*	*Sex*	*Hematocrit*	*ESR*	*Diagnosis*
J1	81	M	49	48	Recent myocardial infarction
J2†	38	M	48	4	Recent myocardial infarction
J3	61	M	50.5	22	Old myocardial infarction
J2*†	38	M	48	2	Old myocardial infarction
J6	67	M	45	36	Recent myocardial infarction
J6	67	M	45	—	Old myocardial infarction
J8‡	89	M	46	37	Ischemic heart disease and angina
J9	50	M	48	7	Recent myocardial infarction
J10	51	M	45	8	Old myocardial infarction with angina
J13	69	M	56.5	1	Old myocardial infarction
J14	45	M	40.5	7	Old myocardial infarction
J15	47	M	46.5	—	Recent myocardial infarction
J16‡	60	F	43.5	2	Femoral artery occlusion and recent myocardial infarction
J17	60	M	48	8	Old myocardial infarction
J18	48	M	51	4	Ischemic heart disease and angina
J26	54	M	55	2	Recent myocardial infarction
J29	51	M	51	6	Ischemic heart disease and angina
J34§	51	M	40	12	Recent myocardial infarction
J48	39	M	40	20	Recent myocardial infarction
J137	71	F	40	62	Recent myocardial infarction and hypothyroid
J145	49	M	45.5	11.5	Recent myocardial infarction
J27	75	M	50	8	Arteriosclerosis and angina
J36	59	F	35	31	Ischemic heart disease and angina

Note: All infarcts older than 2 weeks are described as old.
*Donor was tested repeatedly.
†Patient died 6 months after test.
‡Patient was treated for congestive heart failure.
§Patient died fortnight after test.

Table IV Laboratory data on patients suffering from arterial disease

Code	*Age (yr.)*	*Sex*	*Hematocrit*	*ESR*	*Diagnosis*
C7	36	M	61	1	Cerebral thrombosis
B19	60	F	—	68	Cerebral thrombosis
S22	60	M	47	8	Arteriosclerosis obliterans
S24	41	M	46	59	Femoral artery occlusion
S25	38	M	—	—	Femoral artery embolus
S35	58	M	47	25	Cerebral thrombosis
S39*	35	M	—	—	Buerger's disease
S40*	63	M	44	—	Arterial thrombosis, arteriosclerosis obliterans
S41	63	M	48	9	Arterial peripheral thrombosis, diabetes mellitus

*Patient was tested repeatedly, at intervals of several days or weeks.

fluid laminae or of the surfaces surrounding the fluid and of the geometry of these surfaces. In the simplest case of two parallel surfaces, spaced by a gap d and moving at a relative velocity V, the velocity gradient between these surfaces is equal to V/d (the units of velocity, cm./sec., are divided by the units of distance, cm., in order to yield the units of the rate of shear, sec.$^{-1}$).

The term "thixotropic" describes a system in which viscosity depends on the

time and the rate of shear increasing with the increasing rate of shear A thixotropic system is reversible the thixotropic recovery time ranging from a microsecond to a number of hours, depending on the instrument and method of testing and on the intrinsic properties of the material tested The presence of thixotropy in suspensions or emulsions indicates aggregation (flocculation) of the suspended particles.

The fundamental unit of (dynamic) viscosity is a poise which is equal to 100 centipoises One centipoise corresponds to the viscosity of water at 20° C

Results

The experimental data on blood viscosity are given in Figs. 3 4 and 5 Blood viscosities at any constant rate of shear were found to be distributed in a log normal manner Statistical data are given in Table V and Fig 6 It is interesting to observe that the viscosity values, within limits of standard deviations are partially superimposed at high rates of shear but progressively separate at low rates of shear when groups of normal subjects and groups

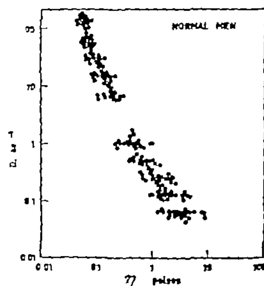


Fig 4 Viscosity of blood in normal men. Circles represent experimental points obtained by means of the cone-in-cone viscometer at 37° C. Viscosity of freshly shed blood was determined first at low rates of shear and then at progressively increasing rates of shear Coordinates the rate of shear D in reciprocal seconds, and the viscosity η in poises.

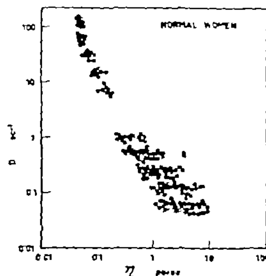


Fig 3 Viscosity of blood in normal women. Circles represent experimental points obtained by means of the cone-in-cone viscometer at 37° C. Viscosity of freshly shed blood was determined first at low rates of shear and then at progressively increasing rates of shear Coordinates the rate of shear D in reciprocal seconds and the viscosity η in poises.

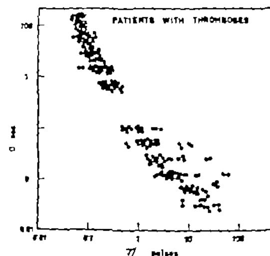


Fig. 5 Viscosity of blood in patients suffering from myocardial infarction and occlusive arterial disease. Circles represent experimental points obtained by means of the cone-in-cone viscometer at 37° C. Viscosity of freshly shed blood was determined first at low rates of shear and then at progressively increasing rates of shear Coordinates: the rate of shear D in reciprocal seconds, and the viscosity η in poises.

Table V. Blood viscosities in normal subjects and in patients determined over a range of rates of shear (viscosity in poises)

	Rate of shear (sec.⁻¹)					
	0.01	*0.1*	*1*	*7.2*	*[illegible]9*	*115*
Normal men						
n	30	30	30	1	1	1
$\bar{x}$	9.9	1	0.45	0.31	0.10	0.056
$\bar{x} \pm s$	4.4–22.1	1.13–3.93	0.[illegible]–0.82	0.11–0.22	0.0[illegible]–0.13	0.045–0.0[illegible]5
$\bar{x} \pm 2s$	1.9[illegible]–49.4	0.60–7.35	0.15–1.41	0.0[illegible]–0.31	0.06–0.1	0.041–0.0[illegible]6
Normal women						
n	42	42	42	10	10	10
$\bar{x}$	11.9	2.[illegible]	0.41	0.13	0.0[illegible]	0.045
$\bar{x} \pm$	4.9–28.6	1.23–3.94	0.25–0.57	0.09–0.18	0.06–0.08	0.045–0.051
$\bar{x} \pm 2s$	2.0–[illegible]5	0.69–[illegible]0	0.19–0.8[illegible]	0.06–0.[illegible]6	0.05–0.09	0.043–0.054
Patients						
n	39	39	39	2[illegible]	[illegible]9	26
$\bar{x}$	57.5	7.23	1.0	0.22	0.10	0.065
$\bar{x} \pm$	21.7–157	3.15–16.7	0.60–[illegible]0	0.16–0.3[illegible]	0.08–0.14	0.041–0.101
$\bar{x} \pm 2s$	7.8–425	1.3[illegible]–35.3	0.[illegible]4–4.0	0.11–0.45	0.06–0.19	0.0[illegible]6–0.158

The data were calculated from log-normal distributions. Number of tests. $\bar{x}$ Arithmetic mean. s Standard deviation.

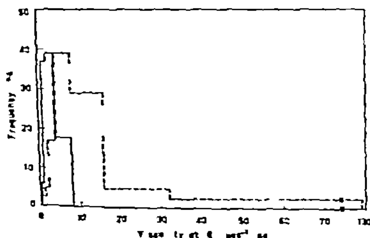


Fig. 6. Histogram for blood viscosities in normal subjects and in patients. The full line represents a histogram for normal men and normal women. The broken line represents a histogram for patients suffering from myocardial infarction and occlusive arterial disease. Frequencies were defined in ranges 0–0.49 poise, 0.5–0.99 poise, 1–1.99 poise, 2–3.99 poise, 4–7.9 poise, 8–15.9 poise, 16.0–31.9 poise, 32–63.9 poise, and 64–128 poise in order to correspond with the log-normal distribution of viscosities.

of patients are compared. In order to elaborate these findings, a histogram (Fig. 6) has been prepared for viscosity values determined at 0.1 sec.⁻¹ Since the viscosity coordinate is numerical, a most pronounced skewed distribution is evident.

In order to determine whether the age of donors has some effect on the viscosity of blood, it was necessary to plot viscosity against the age of patients and of normal subjects (Figs. 8 and 9). Age has no effect on blood viscosity if this viscosity is tested

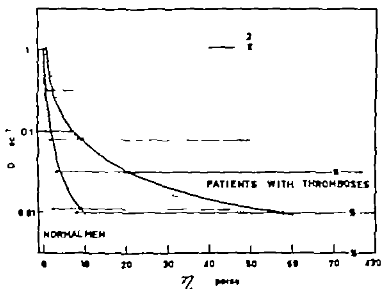


Fig. 7. Arithmetic means and limits of two standard deviations for blood viscosities in normal men and patients. Full lines represent the arithmetic means, x̄. The broken lines represent the 95 per cent confidence limits (actually x̄ ± 2s). Arrows indicate the spread of data for men or for patients, respectively. Coordinates: the rate of shear D in reciprocal seconds and the viscosity η in poises.

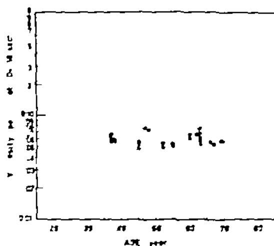


Fig. 8. Viscosities of blood plotted as a function of the donor's age. Open dots indicate blood viscosities of normal men, and closed dots indicate blood viscosities of patients. All viscosity data were determined at the rate of shear of 118 sec.$^{-1}$ Coordinates: viscosity in poises and age in years.

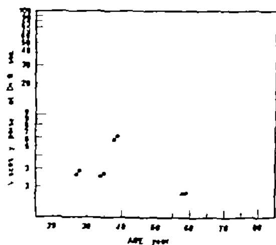


Fig. 9. Viscosities of blood plotted as a function of the donor's age. Open dots indicate blood viscosities of normal men and closed dots indicate blood viscosity of patients. All viscosity data were determined at 0.1 sec.$^{-1}$ Coordinates: viscosity in poises and age in years.

at high rates of shear. Also, the age of the donor has no effect on the blood viscosity tested at low rate of shear when this donor belongs to a normal group. However, when the viscosities of *both* the normal subjects and the patients are viewed, all data being obtained at low rates of shear, then the over-all picture appears to indicate that blood viscosity is related to the age of the total population.

Clotting times of blood were determined and the data are summarized in Table VI.

Table VI. Summary of data on clotting time of blood in normal men and in patients

	Normal men	Patients
Clotting time determined at 0.51 sec.$^{-1}$		
n	42	42
$\bar{x}$	2 min. 42 sec.	3 min. 15 sec.
$\bar{x} \pm s$	2 min. 8 sec. — 3 min. 28 sec.	2 min. 32 sec. — 4 min. 10 sec.
$\bar{x} \pm 2s$	1 min. 40 sec. — 4 min. 28 sec.	1 min. 58 sec. — 5 min. 22 sec.
Clotting times determined at 59 sec.$^{-1}$		
n	41	43
$\bar{x}$	2 min. 22 sec.	2 min. 22 sec.
$\bar{x} \pm s$	1 min. 58 sec. — 2 min. 53 sec.	1 min. 56 sec. — 2 min. 55 sec.
$\bar{x} \pm 2s$	1 min. 37 sec. — 3 min. 30 sec.	1 min. 35 sec. — 3 min. 35 sec.
Calculated ratios of individual clotting times determined at 0.51 and 59 sec.$^{-1}$		
n	25	42
$\bar{x}$	1.13	1.405
$\bar{x} \pm s$	0.955 — 1.33	1.22 — 1.70
$\bar{x} \pm 2s$	0.805 — 1.58	1.01 — 2.06

The data were calculated from log-normal distribution. n: Number of tests. $\bar{x}$: Arithmetic mean. s: Standard deviation.

Clotting times have been determined in each case, both at low rate of shear (0.51 sec.$^{-1}$) and at high rate of shear (59 sec.$^{-1}$). It is evident that the clotting time of patients is longer than the clotting time of normal subjects. This phenomenon will be considered in the discussion section. The ratio of clotting times determined at low and at high rates of shear was calculated in each individual case, and the summary of results is also given by Table VI. This ratio is higher in the group of patients than in the group of normal subjects, the significance of which is that the clotting process accelerates more rapidly with increasing rate of shear in the blood of the patients than in the blood of the normal donors.

Hematocrit data were obtained by the usual methods, with a microcentrifuge being used. The hematocrits are given in Tables I, II, III, and IV. The arithmetic means and standard deviation were calculated and are as follows: *Normal men*: $\bar{x}$ = 45.7 per cent, $\bar{x} \pm s$ = 42.7 to 48.8 per cent, $\bar{x} \pm 2s$ = 40.0 to 52.2 per cent. *Normal women*: $\bar{x}$ = 40.7 per cent, $\bar{x} \pm s$ = 39.7 to 42.7 per cent, $\bar{x} \pm 2s$ = 36.9 to 44.9 per cent. *Patients*: $\bar{x}$ = 47.0 per cent, $\bar{x} \pm s$ = 41.7 to 52.3 per cent, $\bar{x} \pm 2s$ = 37.2 to 58.8 per cent. There is no pronounced difference between normal subjects and patients.

Erythrocyte sedimentation rates have been determined by means of the usual Westergren method. ESR values are given in Tables I, II, III, and IV. The arithmetic means and standard deviations were calculated and are as follows: *Normal men*: $\bar{x}$ = 2.9 mm./hour, $\bar{x} \pm s$ = 1.1 to 7.9 mm./hour, $\bar{x} \pm 2s$ = 0.4 to 21.5 mm./hour. *Normal women*: $\bar{x}$ = 4.4 mm./hour, $\bar{x} \pm s$ = 2.3 to 8.4 mm./hour, $\bar{x} \pm 2s$ = 1.2 to 16 mm./hour. *Patients*: $\bar{x}$ = 10.3 mm./hour, $\bar{x} \pm s$ = 2.8 to 37.4 mm./hour, $\bar{x} \pm 2s$ = 0.75 to 139 mm./hour.

Both the ESR and the hematocrit values were calculated on the basis of log normal distributions.

Discussion

Discussion of the results will proceed under the following headings: viscosity of blood: a general pattern; clotting time of blood; relevance of this study as a clinical diagnostic tool.

1. Viscosity of blood: a general pattern. Viscosity of blood is confirmed to be dependent on the rate of shear and to decrease as the rate of shear increases. This decrease is reversible, and the recovery of the original value of viscosity proceeds at a certain finite rate at low velocity gradients, although it is nearly instantaneous at high velocity gradients.

Table VII. Comparison of the spread of experimental viscosities with the calculated spread of viscosity data estimated from the spread of hematocrit values

Donors	Experimental viscosities		Calculated viscosities*
	Ratios of viscosities $(\bar{x} + s)/(\bar{x} - s)$†		Ratios of viscosities corresponding to hematocrits at one standard deviation
	At 0.1 sec.$^{-1}$	At 118 sec.$^{-1}$	At any rate of shear
Normal men	3.5	1.35	1.23
Normal women	3.2	1.12	1.10
Patients	5.3	2.43	1.43
	Ratios of viscosities $(\bar{x} + 2s)/(\bar{x} - 2s)$†		Ratios of viscosities corresponding to hematocrits at two standard deviations
	At 0.1 sec.$^{-1}$	At 118 sec.$^{-1}$	At any rate of shear
Normal men	12	1.85	1.50
Normal women	10	1.27	1.28
Patients	28	6.0	2.0

*Viscosity was calculated using an equation $\eta = 70 \log \nu$, which was estimated from the data of Haynes.[8]
†Values $\pm s$ and $\pm 2s$ were taken from Table V.

Since a difference is observed in the viscosity data in normal subjects and in patients, an attempt is made to account for this difference, and also to account for the spread of viscosity data in general. At high rates of shear, the spread of viscosity data in normal men and normal women is entirely accounted for by the spread of their hematocrit values. This is evident from Table VII, in which the experimental viscosities (limits of one standard deviation) are shown to be equal to viscosities calculated from the hematocrit values (also at limits of one standard deviation). In the case of patients, however, the spread of viscosities cannot be accounted for entirely by the spread of their hematocrits. The spread of blood viscosities at low rates of shear, for both the normal subjects and the patients, cannot be accounted for by a spread in the hematocrit values.

The slight relative elevation of blood viscosity determined at high rates of shear in patients, as compared with normal subjects (noted also recently by Mayer[7] and Eisenberg[8]), although insignificant if compared with the great elevation observed at low rates of shear, might be due to certain variations in the plasma viscosity. This could be suggested by the work of Shinagawa,[9] who found that viscosities of sera in coronary diseases are about 5 per cent greater than viscosities of normal blood sera.

The difference in means of the whole blood viscosities, at low rates of shear in patients and normal subjects can be explained only by the difference in the degree of aggregation of the red cells. The increased aggregation of the red cells in thrombotic states can be due to a number of causes. Most probable are the elevation of lipids or fibrinogen,[10-12] modifications of the surface properties of the red cells,[14,15] or the presence of toxins.[16]

Whatever the causes for aggregation of the red cells, the fact remains that the viscosities of blood in normal subjects and in patients differ significantly. A *t* value test calculation (Table VIII) has been carried out in order to ascertain whether the blood viscosities of normal subjects do belong to the same population distribution as the blood viscosities of patients. The probability of their being a part of the same (statistical) population is less than one in a million if viscosities are determined at low rates of shear.

The blood viscosities of subgroups of patients were also compared. Viscosity of blood in occlusive arterial disease was tested against the viscosity of blood in myocardial infarction, or the latter was tested against angina, or acute infarcts were tested against the old infarcts. The results indicate that all these subgroups belong to a single population distribution (from the viewpoint of blood viscosity).

Table VIII. Summary of t-tests concerning the probability that two groups of donors belong to the same population distribution (of viscosity)

Groups	Rate of shear (sec⁻¹)	Σn	t	p	Comments
Normal men vs. patients	0.01	69	8.1	< 0.0001	Most significant
	0.1	69	5.6	< 0.001	Most significant
	1.0	69	5.2	0.001	Most significant
	118	41	4.12	0.001	Most significant
Normal women vs. patients	0.01	81	7.9	< 0.0001	Most significant
Acute infarcts vs. old infarcts	0.01	17	1.77	0.1	Not significant
Acute infarcts vs. arterial thrombosis	0.01	22	0.99	> 0.1	Not significant
Angina vs. infarcts	0.01	17	0.61	> 0.1	Not significant

The important conclusion is that the blood viscosity in patients suffering from myocardial infarction and occlusive arterial disease is much greater than the blood viscosity in normal men and women if such viscosity is tested at low rates of shear. As can be seen from Fig. 7, the 95 per cent confidence limit for blood viscosity of normal men is just below the arithmetic mean of blood viscosities of patients.

It is well known that ESR values are elevated in some thrombotic states. Results of individual ESR tests have been correlated with the corresponding individual blood viscosities, the correlation[17] analysis giving the value of r as 0.457, with the significance level of 0.02. Unfortunately, as is also well known, the very wide spread of ESR values does not allow their application as a specific test.

Finally, an answer should be given to a question: How do the low rates of shear discussed in this study compare with rates of shear encountered in vivo? The principal distinction between flow in the rotational cone-in-cone viscometer and flow in a circular vessel lies in the fact that the former is characterized by a homogeneous velocity gradient; flow in a circular vessel, on the other hand, is characterized by a profile of flow velocities and a profile of velocity gradients, the latter of which requires a zero rate of shear in the axis of the vessel and a certain maximum rate of shear at the vessel wall. Consequently, in any vessel in vivo or in vitro, the rates of shear will vary from zero at the axis of the vessel to some maximum value (at the wall) of, for instance, 10 or 100 sec⁻¹; the actual numerical values of the maxima depend on the size of the vein or artery. These maxima vary in time, depending on the cardiac output, and vary even during the duration of a single pulse.

The axial flow region in vessels corresponds to the low rates of shear. Also, any stasis-like conditions would bring about a widespread decrease in the rates of shear up to zero values.

Since the viscosity of blood is dependent on rate of shear, a profile of viscosities also exists, the maximum viscosity being in the axial region of the vessel, and the minimum viscosity being in the region adjacent to the wall.

It was stated earlier that the viscosity of blood depends greatly on the degree of aggregation of the red cells. Whatever is the mechanism responsible for the adhesive properties of the red cells, the degree of aggregation at any particular time, and thus the size of an aggregate at any particular time, depends on the conditions of flow. That is, the size of an aggregate depends on the rate of shear. In a homogeneous field of rates of shear, as in the cone-in-cone viscometer, the degree of aggregation assumes a certain value characteristic of the sample of blood, and is large at low rates of shear and progres-

sively decreases as the rate of shear increases. A single and unique value of aggregation corresponds to a certain constant rate of shear. This is not the case during flow in circular vessels. Since flow in circular vessels is characterized by a profile of velocity gradients, the degree of aggregation of the red cells is greatest in the axis and lowest at the wall of the vessel.

Determination of blood viscosities at very low rates of shear (0.01 to 1 sec.$^{-1}$) permits (a) an estimation of the degree of aggregation of the red cells as it might be encountered in the axial stream or in the near stasis conditions and (b) an estimation of *resistance* to flow. Here we might add that viscosity is in essence a measure of internal friction.

Although an estimation of the aggregation of red cells can be carried out visually (by means of microscopes, movie cameras, etc. in vivo and in vitro) it is purely qualitative; on the other hand results obtained by means of the cone-in-cone viscometer are quantitative and are expressed in fundamental units.

2. *Clotting time of blood.* The clotting times of blood determined by means of the cone-in-cone viscometer were found to decrease with increasing rates of shear. These results confirm earlier reports.[2,11,13] However, the observation that clotting times determined at low rates of shear are *longer* in patients with cardiovascular diseases than in normal subjects is especially interesting in view of reports by Goldrick and Whyte[29] and Goldrick[31] that the clotting time in New Guinea natives is shorter than the clotting time in Australians.

A statement that clotting time is shorter in normal subjects than in patients appears, at first sight, to contradict the established ideas. This is not necessarily so. The usual laboratory tests require the measurement of clotting time until the moment at which a solid clot is formed in the glass tube. In our tests the clotting time is measured only to the point at which blood viscosity starts to increase. It is quite probable that there is a pronounced difference between the time taken by gel formation in the blood of normal subjects and that in the blood of patients, the latter being much shorter. Were this true, the contradiction could be resolved.

A second interesting point is that the individual ratios of clotting times at low and at high rates of shear differ most significantly, being higher in patients than in normal subjects. This might illustrate the increased response of coagulation processes to the velocity gradient in thrombotic states, and could be related, perhaps, to the known response of platelets, which aggregate the more profusely the higher is the velocity gradient.[18,32,33]

A *t* test calculation was carried out and the results are as follows: comparison of clotting times in normal subjects and patients $t = 2.76$, $p < 0.01$; comparison of clotting ratios in normal subjects and patients $t = 19.7$ and $p =$ ca. 0.0001.

3. *Relevance of this study as a clinical diagnostic tool.* The crucial point of this study is to show in what relation resides the viscosity (rheology) of blood in respect of thrombotic states and etiology of thrombosis. It cannot be denied that an elevated viscosity of blood, as determined at low rates of shear, is associated *with thrombotic states. The present retrospective study shows* (a) that there *is no significant difference between blood viscosity* in coronary and arterial diseases, (b) that there is a most significant ($p =$ ca. 0.000 001) difference between the blood viscosity of normal subjects and that of patients (blood viscosity being determined at low rates of shear) and (c) that there is no increase in blood viscosity with age unless a thrombotic state sets in.

The outline of the following discussion contains three basic thoughts: (a) that *increased viscosity of blood might precipitate coronary* or arterial disease, (*b*) that arterial disease or coronary infarction might encourage an increased viscosity, and (c) that a vicious circle might occur: arterial disease inducing higher viscosity and higher blood viscosity leading to progress of arterial disease and vice versa.

An increase in the viscosity of blood leads *to a slowing of the circulation. It is* well known[33] that a slowing of the circulation *leads to conditions that favor thrombosis*, probably because of two factors: (a) platelets, which under normal conditions of flow move along the axial stream

drift to the walls of vessels and (b) if any thrombus is formed a predisposition exists for such thrombus to propagate. Such conditions could follow an increase in viscosity due to an increased aggregation of red cells. Once a thrombus is formed an increase in the vascular resistance slows further the rate of flow decreases the velocity gradient, and further increases the viscosity.

Aggregation of the red cells (as indicated by shear-dependent viscosity and thixotropy) will always take place when the rate of shear is below a certain critical value, and such a value is not reached in the axial stream of many vessels. Aggregates may intermittently plug the entrances to arterioles[19] and cause a local stasis. A localized hypoxia may lead through local changes in blood pH to an increase in the local blood viscosity and the internal viscosity of the red cell.[20-27]

Thus, although it appears that increased viscosity of blood may well contribute to vascular occlusion it should be noted that direct evidence that coronary diseases are secondary to changes in viscosity is not yet available.

If coronary and arterial diseases were secondary to changes in viscosity we would expect to find changes in viscosity before we encountered the clinical manifestations of disease. This study still remains to be done and thus, no answer is yet available.

Summary

Viscosity of blood obtained by venepuncture from normal subjects and from patients suffering from myocardial infarction and arterial thrombosis has been studied by means of a cone-in-cone trolley viscometer.

Viscosity of blood in patients was found to be appreciably higher than in normal control subjects especially at very low rates of shear (about 0 1 sec.$^{-1}$) the difference being more than fivefold. Statistical analysis indicated that the chance of these two sets of viscosity data being drawn from a single population distribution is less than one in a million.

The dispersion of viscosity data at high rates of shear may be accounted for by dispersion in hematocrit values. The dispersion of viscosity data at low rates of shear cannot be accounted for by a spread of hematocrit values and is attributed to the aggregation of the red cells.

Blood viscosity of normal donors is not affected by their age. However if the blood viscosities of both normal subjects and patients are viewed together then a pattern appears in which viscosity (determined at low rates of shear) increases with the age of the donors, although this is due to increasing occurrence of disease with increasing age of the donor.

Clotting times of blood measured at low rates of shear are significantly longer for patients than for normal subjects.

This study confirms without any doubt, that elevated viscosity of blood at low rates of shear is associated with and symptomatic of thrombotic states.

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Complications in 1,056 investigations of the left side of the heart

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Since 1950 investigations of the left side of the heart have gradually become a routine procedure in the diagnosis of cardiac disease, first by means of retrograde arterial catheterization,[21] later through percutaneous puncture of the heart and the great vessels,[1,8,9,13] and since 1959 through puncture of the interatrial septum.[7,16,17]

The purpose of the present paper is to give a report on the complications met with during investigations of the left side of the heart by all commonly used methods in one laboratory.

Material

During the last 10 years (from March 1955 until February 1965) 1,056 examinations of the left side of the heart have been performed in 726 patients in this laboratory (Table I). Most of the patients have been adults and older children. Only 54 of the patients were less than 15 years of age.

The present report comprises all examinations in which the heart, the interatrial septum, or just one of the great vessels was punctured, whether the investigation was successful or not. The distribution on diagnosis is seen in Table II.

Sixty of the investigations were concluded with angiocardiography in collaboration with the Department of Diagnostic Radiology. An analysis of the complications of selective angiocardiography has been published previously by Davidsen and associates.[6]

Methods

The percutaneous punctures of the heart and great vessels have been performed using the method of Radner[13] with a slightly modified Brock technique[3] as described by Tybjaerg Hansen and associates.[19]

The retrograde catheterizations of the left side of the heart have been performed by means of catheters inserted most often into the femoral artery, employing the technique of Seldinger.[14]

The transseptal left heart catheterizations have been performed using the method developed by Ross[1,7] with modifications as described by Lindeneg and associates.[12]

Complications

In 1,056 examinations of the left side of the heart, complications were encountered during 149 investigations (14.1 per cent).

I. Complications of suprasternal and/or transthoracic left ventricular punctures. These examinations were carried out 832 times. Complications were seen 102 times in 92 investigations (11 per cent).

A. COMPLICATIONS DUE TO LESIONS FROM

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Table I. Distribution of 1 056 investigations of the left side of the heart

Investigative procedure	*Number*	*Time of beginning in this laboratory*
Suprasternal puncture	570	March 1955
Transthoracic left ventricular puncture	17	April, 1957
Simultaneous suprasternal and left ventricular puncture	245	April 195
Retrograde arterial catheterization	72	January 1960
Transseptal left heart catheterization	152	December 1960
Total	1 056	

Table II. Distribution on diagnosis of 726 patients examined

Diagnosis	*Number of patients*
Rheumatic mitral disease	388
Rheumatic aortic disease	92
Combined rheumatic valvular disease	74
Other acquired heart diseases	34
Congenital aortic stenosis and/or incompetence	71
Other congenital heart diseases	46
No heart disease	21
Total	726

THE NEEDLES. These occurred in 67 cases (Table III).

Fatalities. In one case death followed on the third day after the investigation.

Case No. 5519. This 41-year-old man, desperately ill with rheumatic aortic stenosis, had severe untreatable left heart incompetence. An uneventful simultaneous suprasternal and percutaneous left ventricular puncture was performed. On the second day x-ray examination revealed a slight pneumothorax, pneumopericardium, pleural effusion, and a more pronounced enlargement of the heart, but there were no clinical signs of cardiac tamponade. He was treated with digitalis, diuretics, and meperidine but died suddenly on the third day. Autopsy revealed a few hundred cubic centimeters of clear fluid in each pleural sac. The left ventricle was considerably enlarged and the wall was thickened. The aortic valves were grossly calcified and the lumen was only 1 by 8 mm. in size. (This case was published previously by A. Tybjaerg Hansen and associates.[14])

Mediastinal hematoma was seen on x-ray examination in 29 cases. In 3 cases the administration of meperidine was necessary because of thoracic pains. The other patients had no symptoms at all.

Pericardial hemorrhage was noticed on x-ray examination in 17 cases. In one case there was a slight pneumothorax as well. Only one case was accompanied by symptoms (*see later* Case No. 5478). In 3 instances a small pericardial hemorrhage that was observed during operation was evident until 2 months later.

Pneumothorax was encountered 11 times. In 2 cases (one being Case No. 5519)

Table III. Complications due to lesions from the needles in 832 suprasternal and/or transthoracic left heart punctures

Complication	*Number*	*Symptoms (number)*	*Duration*			*Treatment (number)*
			Days	*Weeks*	*Months*	
			(number)			
Mediastinal hematoma	29	3	29			3
Pericardial hemorrhage	17	1		14	3	1
Pneumothorax	11	2	11			2
Hemothorax	5		5			1
Perforation of trachea	2	1				
Perforation of a coronary artery	2	1				
Fatalities	1					
Totals	67					7

x-ray examination showed a slight pneumopericardium as well. One patient had thoracic pain and was treated with meperidine. Only one case was severe, with total pneumothorax on one side.

Case No. 5145. This 54-year-old man had aortic stenosis. A few minutes after combined suprasternal and left ventricular puncture he suddenly felt thoracic pain on respiration and became cyanotic. X-ray examination revealed a total pneumothorax on the left side. He was treated with oxygen and exsufflation of 1,700 c.c. of air. There was complete recovery in a few days. (This case was published by Tybjaerg Hansen and associates.[19])

Hemothorax occurred 5 times. All cases were slight. In one, penicillin was administered as a prophylaxis.

Perforation of the trachea occurred twice. One of the patients suffered spasms of the larynx but recovered within a few minutes. There were no late sequelae.

Perforation of a coronary artery occurred twice during left ventricular puncture. In both cases the examination was terminated. One patient developed bradycardia and a slight drop in blood pressure for a few seconds. In neither case were changes in the electrocardiogram, x-ray film, or serum glutamic oxaloacetic transaminase (SGOT) registered during the following days.

II. CARDIAC IRREGULARITIES AND CONDUCTION DISTURBANCES. These were seen 8 times (Table IV).

Supraventricular tachycardia was seen 3 times. One instance lasted 3 minutes and disappeared spontaneously. The other 2 instances lasted for 2 days and were succeeded by inversions of the T waves.

Case No. 5478. This 9-year-old boy had aortic stenosis. Attempts to puncture the left ventricle under general anesthesia were made three times, with no success. Fifteen minutes after recovering from the anesthesia, he experienced a sudden drop in blood pressure and developed tachycardia. He was treated with blood transfusions. The ECG showed inverted T I, II, III and elevation of S-T V3-4. The sedimentation rate and SGOT were elevated. X-ray examination showed pericardial effusion. The patient complained of fatigue and precordial pains. All symptoms disappeared after 6 days. (This case was published by Tybjaerg Hansen and associates.[19])

Case No. 3416. This 50-year-old woman had mitral stenosis. After suprasternal puncture, during which accidentally only the right ventricle was punctured, a sample of blood from the femoral artery was taken. Following this there was prolonged bleeding. After 30 minutes of compression of the artery there was a sudden drop in blood pressure, which was treated with atropine. Two hours later there was another fall in blood pressure which was accompanied by supraventricular tachycardia. After treatment with procainamide, various heart arrhythmias occurred and the blood pressure was unobtainable. She was then treated with infusions of pressor amines for 24 hours. The body temperature and SGOT were elevated for a few days. Two days later the ECG showed inversion of T I, II, III which still persisted 20 days later. (This case was published by Tybjaerg Hansen and associates.[19])

Ventricular tachycardia was encountered twice; both lasted a few seconds. One instance occurred during suprasternal puncture in a patient suffering from mitral stenosis. The other occurred during the second attempt at left ventricular puncture after a suprasternal puncture. The patient

Table IV. Cardiac irregularities and conduction disturbances during 832 suprasternal and/or left heart punctures

Complication	Number	Duration: Seconds	Duration: Minutes	Duration: Days	Treatment (number)
		(number)			
Supraventricular tachycardia	3		1	2	2
Ventricular tachycardia	2	2			
Ventricular fibrillation	1	1			
Bundle branch block	1		1		1
Heart arrest	1	1			
Totals	8				

suffered from acquired aortic stenosis and incompetence

Ventricular fibrillation during combined puncture occurred twice in the same patient suffering from acquired aortic stenosis and incompetence It lasted from 2 to 3 seconds each time

Right bundle branch block was seen once during simultaneous suprasternal and left ventricular puncture The patient was a 41 year-old woman with rheumatic mitral incompetence It was accompanied by a slight fall in blood pressure and a slow pulse. All symptoms disappeared after 1 mg of atropine had been administered intravenously

Heart arrest occurred during one examination

Case No 5173 This 33-year-old man had acquired aortic stenosis. Immediately after combined suprasternal and left ventricular puncture the patient became unconscious, with a slow pulse followed by heart arrest for 10 seconds. He recovered spontaneously but complained of retrosternal pains for 2 days. There were no alterations in the x-ray film (This case was published by Tybjaerg Hansen and associates.[19])

C OTHER COMPLICATIONS Other complications were encountered 27 times (Table V)

Vasovagal attacks occurred 9 times. One attack was in connection with a right bundle branch block, one preceded heart arrest and one followed accidental puncture of a coronary artery All patients suffered from rheumatic heart disease Five patients were treated with atropine 1 mg intravenously

Fall in blood pressure was seen 8 times. In 5 cases it was of lesser grade. Three patients had longer lasting hypotension which in 2 was in connection with other complications (Case No 5478 and 3416) The third case is as follows

Case No 3801 This 45-year-old woman was seriously ill from combined rheumatic mitral and aortic valvular disease. During combined puncture the right as well as the left ventricle was punctured. Five minutes later there was collapse She was treated with pressor amines for 3 days after which the blood pressure was stable. There were no changes in the ECG or x-ray film. SGOT was slightly elevated for 1 week (This case was published by Tybjaerg Hansen and associates.[19])

Pulmonary edema occurred after simultaneous puncture in one man, 49 years old with mitral stenosis and incompetence who was in a state of slight cardiac incompetence. He recovered after meperidine was administered 50 mg intravenously

Thromboembolic complication was encountered once

Case No. 3346 This 56-year-old woman had mitral stenosis and aortic incompetence. She had atrial fibrillation but was not on anticoagulation therapy On the day after an uneventful suprasternal puncture there were sudden pains and lividity in the left leg and no pulsation in the femoral artery An embolus 5 cm long, was removed from the femoral artery and normal circulation was re-established within 2 hours. There were no late sequelae

II Complications in connection with retrograde catheterization of the left side of

Table V Other complications to 832 suprasternal and/or left heart punctures

Complication	Number	Duration: Minutes (number)	Duration: Days (number)	Treatment (number)
Vasovagal attack	9	9		5
Hypotension	8	6	2	3
Pain	7	5	2	7
Pulmonary edema	1	1		1
Embolism	1			1
Febrile reaction	1		1	
Totals	27			17

Table VI Complications during 72 retrograde catheterizations of the left heart

Complication	Number	Duration		Treatment (number)
		Minutes	Days	
		(number)		
Hematomas or prolonged bleeding	7	2	5	4
Vasovagal attack	3	3		2
Conduction disturbances	3	3		
Thrombosis	1		1	1
Pain and paresthesia	1		1	
Totals	15			7

the heart. These occurred 15 times in 15 of 72 examinations (21 per cent) (Table VI)

HEMATOMAS. Five patients developed hematomas around the artery after the catheter had been removed None showed disturbances in the bleeding and coagulation system. In one case, meperidine was given because of pain and in another ultrasound was administered because the hematoma was of considerable size.

BLEEDING. In 2 patients the bleeding could not be stopped by compression of the femoral artery which in both cases had to be sutured. Anticoagulant therapy was given afterward In one of these cases, thrombosis occurred 3 days after the operation and embolectomy was performed successfully There were no late sequelae.

VASOVAGAL ATTACKS. These occurred in 2 patients with congenital subvalvular aortic stenosis, and in 1 patient with rheumatic mitral stenosis and incompetence. Two of the patients were treated with atropine, 1 mg intravenously The examinations were continued without further complications.

CONDUCTION DISTURBANCES. These were seen 3 times. Supraventricular tachycardia occurred in one instance and ventricular tachycardia in another as the catheter was advanced into the left ventricle these arrhythmias ceased after a few seconds as the catheter was withdrawn The third case was as follows

Case No 5699 This 41 year-old woman had left-sided incompetence of unknown etiology A Teflon catheter happened to be passed into one of the coronary arteries but was promptly withdrawn. During the next 2 minutes the ECG showed various kinds of atrioventricular block. The changes disappeared without treatment, and the examination was continued without further disturbances The SGOT remained normal during the following days.

THROMBOSIS. Thrombosis of the abdominal aorta occurred once

Case No 5696 This 42 year-old woman suffered from mitral incompetence. She was treated with prophylactic anticoagulation therapy diuretics and digitalis The ECG showed normal sinus rhythm Two days after an uneventful retrograde left heart catheterization through the right femoral artery she complained of tenderness and pain in the lower part of the abdomen During the next few days a decreasing pulsation of the right femoral artery and lividity of the right foot were observed A thrombus, 10 cm long, was removed from the abdominal aorta 30 cm. above the site of the puncture. Thereafter pulsations and temperature in the right leg were normal and no signs of arterial insufficiency on effort were evident

PAIN One patient complained for a few days of pains in the cubital region and paresthesia in the median nerve region after retrograde catheterization through the brachial artery The pulsation of the artery was normal

III Complications of transseptal left heart catheterization This investigation was carried out 152 times. Complications were noticed 64 times during 42 examinations (28 per cent) (Table VII)

FATALITIES. In 1 case death followed hemopericardium

Case No 7410 This 7 year-old boy had severe valvular aortic stenosis. One hour after an unevent

Table VII. Complications of 152 transseptal left heart catheterizations

Complication	Number	Duration: Seconds	Duration: Minutes	Duration: Hours	Duration: Days	Treatment (number)
		(number)				
Cardiac irregularities and conduction disturbances	17	3	6	1	7	4
Pain	15	9	5	1		5
Perforation of the myocardium	11					2
(fatalities)	(1)					
Mediastinal hematoma	4				4	
Vasovagal attack	4		3	1		3
Hypotension	3		1	1	1	1
Rise in body temperature	3				3	
Pericardial hemorrhage	3				3	1
Perforation of a pulmonary vein	1					
Embolism	1				1	1
Venous spasm	1		1			1
Hematoma at femoral vein	1				1	
Totals	64					18

ful transseptal heart catheterization he became pale with tachycardia and slightly lowered blood pressure. During the next hours he developed slight enlargement of the liver and a rise in temperature. A roentgenogram showed that the heart had enlarged slightly. Since his condition remained stable no pericardiocentesis was performed during the next 24 hours. When no improvement ensued, however, preparations for thoracotomy were made. He then experienced a sudden cardiac arrest. Open-chest heart massage was performed immediately but in vain. Two hundred cubic centimeters of blood was found in the pericardial sac. At autopsy no lesion was discovered on the outer surface of the heart, but inside the left atrium a small lesion was seen in the endocardium just opposite the site of puncture of the interatrial septum and a minimal perforation had probably been present.

CARDIAC IRREGULARITIES AND CONDUCTION DISTURBANCES. These were seen on 17 occasions.

ATRIAL FIBRILLATION. There were 5 instances of this, 4 of which occurred during the initial right heart catheterization. In the fifth patient the ECG suddenly showed atrial fibrillation 4 hours after an uneventful examination. In one case the arrhythmia ceased simultaneously with the accomplishment of puncture of the interatrial septum. In the other 4 cases the atrial fibrillation was successfully converted with digitalis.

SUPRAVENTRICULAR TACHYCARDIA. This arrhythmia occurred during 5 catheterizations. One instance was in connection with accidental perforation of a lung vein (Case No. 5284) and 3 occurred immediately after the septal puncture, in one of these cases after ventricular tachycardia (Case No. 6323). During one a short run of right bundle branch block was noticed. The first tachycardia lasted 4 days, the second lasted 3 hours, and the other 2 lasted only a few minutes. All disappeared without treatment.

VENTRICULAR TACHYCARDIA. Two patients developed this arrhythmia. In one case it started after the puncture as the catheter was pushed into the left ventricle and ceased as the catheter was withdrawn. In the other case the situation was as follows:

Case No. 6323. This 14-year-old girl had aortic stenosis. As the catheter was being passed into the left ventricle, ventricular tachycardia began, accompanied by a slight fall in blood pressure. The patient complained of pains in the chest. After 2 hours the ventricular tachycardia shifted to a supraventricular tachycardia, which ceased spontaneously after 3 hours.

RIGHT BUNDLE BRANCH BLOCK. This was seen in 2 cases. One instance was in connection with supraventricular tachycardia and the other one occurred shortly after

puncture in a 44-year-old man suffering from coarctation of the aorta. It lasted 2 minutes and disappeared without treatment.

SINUS ARREST This occurred once after septal puncture had been accomplished The catheter was occluded and therefore was withdrawn into the right atrium Immediately after this procedure the sinus arrest occurred. It lasted only a few seconds and ceased spontaneously There were no symptoms.

COMPLETE ATRIOVENTRICULAR BLOCK. This occurred once

Case No. 5068 This 15-year-old boy had congenital mitral disease. As puncture of the septal wall was performed, the ECG suddenly showed complete atrioventricular block, and the examination was discontinued. The patient had no symptoms at all and received no treatment The ventricular rate was 40 per minute. The condition was unaltered during the following days. On the sixth day the ECG showed second-degree atrioventricular block, and on the eighth day it showed normal sinus rhythm.

FIBRILLATION-FLUTTER. This occurred once just after puncture of the femoral vein. The patient had no symptoms and the examination was continued The irregularity ceased as the septum was punctured

PAIN Fifteen patients complained of precordial pain most often in direct connection with puncture of the interatrial septum Four cases are mentioned in relation to other complications (Cases No 5284 6323 6519 and 7379) As to the other 11 patients, 2 were treated with glyceryl nitrate and 3 with meperidine. In most cases the pain lasted only a few seconds and the symptoms did not interfere with the examination except in one case. Five of the patients had previously had typical angina pectoris on exertion.

PERFORATION OF ATRIAL WALL. This occurred 11 times in 9 examinations. In one case the left atrial wall was perforated and the complication was fatal (Case No 7440) In the other cases the right atrial wall was perforated

Case No. 6519 This 16-year-old girl had pulmonary stenosis. During an attempt at transseptal puncture perforation of the posterior right atrial wall occurred twice. The patient felt precordial pain for about 2 minutes and further examination was given up X-ray examination revealed a slight pericardial hemorrhage for 5 days. There were no signs of cardiac tamponade.

Case No. 5284 This 13-year-old boy had congenital subvalvular aortic stenosis and endocardial fibroelastosis. (This is the same patient who 1 year previously had suffered perforation of a pulmonary vein. *See later*). After the puncture, the tip of the catheter was found to be situated in the aorta The patient had no symptoms and there were no alterations in the blood pressure or ECG The catheter was removed without complications under general anesthesia while a team of surgeons stood by in the event of an emergency

Case No. 7379 This 22 year-old man had congenital aortic stenosis. Septal puncture was tried three times and at each attempt the patient felt a short pain in the chest. On the third attempt the needle slid off and perforated the posterior wall of the right atrium. Apart from the short pain there were no symptoms.

In 5 more investigations, perforation of the posterior right atrial wall occurred during attempts at transseptal puncture. Two of the patients suffered from congenital aortic stenosis 1 from acquired aortic stenosis and incompetence 1 from coarctation of the aorta, and 1 had no heart disease. One patient felt a short pain as the wall was perforated whereas the others had no symptoms at all and no alterations were seen on the roentgenograms.

MEDIASTINAL HEMATOMA. This was seen 4 times on x ray examination. One instance was Case No. 5284 In the other cases there were no symptoms.

VASOVAGAL ATTACKS These were seen 4 times. Two instances occurred in connection with puncture of the femoral vein and 2 in relation to the accomplishment of transseptal puncture Three patients recovered after a few minutes in 2 this occurred after atropine 1 mg intravenously The fourth patient was treated with pressor amines for 4 hours.

HYPOTENSION Hypotension occurred 3 times. One instance was in connection with ventricular tachycardia (Case No. 6323) The second instance was in a 58-year-old woman who was suffering from cor pulmonale One hour after the transseptal puncture in connection with the puncture of a peripheral artery the patient developed shock. She was treated with pressor amines for 48 hours. The third instance was in a 15-year-old girl who had aortic stenosis. After the examination there was a sudden drop in blood pressure to 80/60 mm. Hg

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The electrocardiogram in tachycardia

Common errors of interpretation

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The development of a digital computer program for analysis of continuous and exercise electrocardiograms has demonstrated discrepancies in logic among clinical electrocardiographers. This paper treats two areas of uncertainty electrocardiographic distortions caused by shift of the base line, and the phenomenon of wave summation.

Base-line artifact

Rhythmic, gradual shifts of the base line are common in exercise tracings usually related to increased depth of respiration. Irregular abrupt alterations in the waves may also be introduced by movement of the electrodes. The clinician monitoring or reviewing the electrocardiogram visually selects areas of minimal distortion. This selection technique is sometimes illogical.

Contrary to the preferences of some readers *apparent* base-line horizontality does not indicate freedom from distortion One must instead demand constancy of base line slope for a minimum of two PQRST complexes.

In Fig 1 complex *A* although the most horizontal is the least stable since it straddles a shift in base-line slope. Visual or manual construction of lines (Fig 1) between corresponding portions of adjoining complexes is a check of "parallelism or constancy of base-line slope but does not eliminate all artifact.

A suitable visual logic for scanning large amounts of electrocardiographic data with artifact exclusion (applicable in all cases except alternating morphologies) is a search for adjacent twin" complexes. The amount of distortion and intercomplex variation considered to be acceptable can then be controlled by allowing degrees of dissimilarity

The top tracing in Fig 2 is an example of an exercise tracing with combined artifacts. Complexes *A* and *B* are the closest twins. They are not identical, however showing differences in the P waves and the S-T segments. Therefore although the undistorted electrocardiogram probably resembles *A* and *B* at this moment, its exact configuration is unclear

The lower tracing in Fig 2 permits more certainty Here the lettered complexes are adjoined "triplets." Individual waves can

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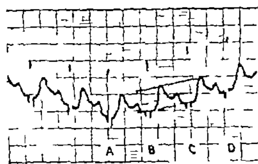


Fig. 1 An example of base-line shift Complexes *B* and *C* exhibit parallelism of major components.

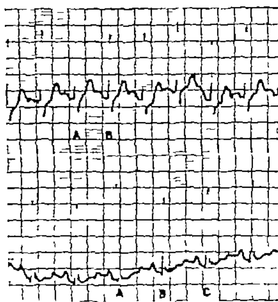


Fig 2 Complexes *A* and *B* (*upper strip*) are nearly identical "twins. Complexes *A* *B* and *C* (*lower strip*) are triplets.

now be measured vertically from the sloping base line

Wave summation

The application of letter designations by electrocardiographers to the various waveforms is more than a simple description of the time voltage curve. It is also an attempt to separate electrocardiographic phenomena When these phenomena coincide the electrocardiographic response is simple voltage summation and the clinician must make subtractions in order to isolate component parts. Examples of this are changes in S and R amplitudes secondary

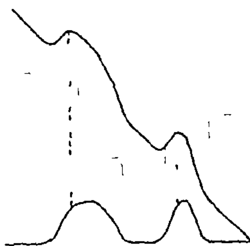


Fig 3 Two dissimilar waves are plotted on a horizontal and a sloping base line Note the apparent shift in the position of the apex.

to shifts of the S-T segment in angina pectoris[1,2] and deviation of the S-T segment due to atrial repolarization forces.

In stress at higher levels of tachycardia no electrocardiographic waves stand alone Important T U and P conglomeration begins at rates around 110 The effects of such summations are interesting and can best be visualized with the aid of a few graphic constructions.

Consider the inscription of an electrocardiographic wave on a linear descending base line. In Fig 3 the horizontally depicted waves have been reconstructed (hand plot arithmetic summation) on the 45-degree base line directly above. Note the shift in time of the wave apexes, and that this alteration in timing is directly related to the broadness of the wave Recall that these changes are all due to the alteration of base-line slope

Consider now a curvilinear base line such as the downslope of a T wave. In Fig 4 curve B has been added to curve *A* to produce curve *C* Component *B* demonstrates a shift in time of the apex as well as an apparent increase in amplitude Construction of a straight line connecting the notch in curve *C* with the return of the

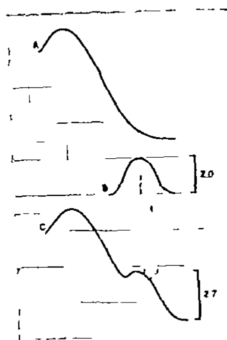


Fig. 4. Curve *A* and curve *B* are summed to form curve *C*. Note the apparent changes in timing and amplitude.

curve to base line will not reproduce the component waves, *A* and *B*. One might argue that an approximate T wave downslope can be inserted here to retrieve *B*. Such an analysis would indeed be possible were it not for the central presence of another deflection, the U wave.

A summated wave with two peaks (commonly called a "T P" wave in tachycardia) can now be required to disgorge three waves. Fig. 5 illustrates three possible combinations. In each case the T, U, and P waves have been plotted by hand to add arithmetically and to form the curve labeled *sum*. Note that the theoretical P amplitude may vary widely and that the notch in the summated curve may not be a precise measure of the end of the T wave. The range of choice is even wider than this display since waves may be asymmetrical and in exercise do not have to retain their "control" shape. (These waveforms are those clearly visible with the usual electrocardiographic amplification and display. The precise low voltage location of the onset and end of the U wave is not known but would not significantly alter the constructions.)

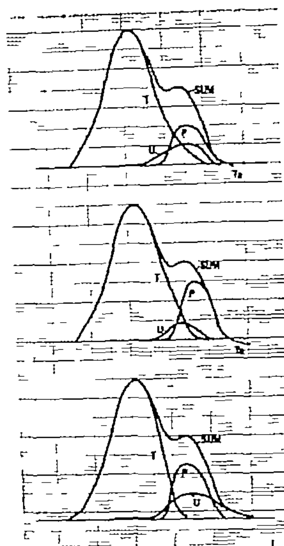


Fig. 5. Three theoretical dissections of a "T-P" wave (*see text*).

Effect on S-T measurement

This wave summation may further obscure the relationship between the P R and S-T segments. When the T, U, and P waves are summated as shown in the third portion of Fig. 5, a sloping P R segment may not be caused by atrial repolarization (T_a) alone. It may be wholly or partially an underlying U wave.[3,4] Thus one of the carefully taught effects of exercise, the increase in P amplitude with visible atrial repolarization, may in some cases or in some part be merely wave summations with no change in atrial electrical activity at all![1]

What then is the least inaccurate method for the measurement of S-T amplitude in the presence of a sloping P R segment? If the downward P R slope is caused by U wave potentials, the P R segment appears to be at or near the end of the U wave. The onset of QRS then becomes the best base line for the entire ST T evaluation. If the P R segment slope in fact represents the forces of atrial repolarization with the QRS inscribed near the center of the T wave (as it usually is) the onset of QRS is again a suitable reference level but only for the J junction. Linear extrapolation of the P R segment through the QRS to establish a lower reference level for the J junction[3,4] would not be appropriate in either case.

The base line for the early S-T segment would therefore be the same. However the effect of atrial repolarization dissipates during inscription of ST T and measurement of the undistorted late ST T amplitudes requires knowledge of its course. A method of estimating the course of atrial repolarization by extending the arc of the P R segment has been proposed.[4] However when there is U wave contribution to the P R segment arc this method can not be employed and the entire S-T segment is again best measured from the QRS onset reference level. P R segment extrapolations can be made with knowledge of the forces shaping the P R segment and the true P amplitude and duration.

Example tracing

Fig 6 is a typical exercise tracing recorded with a single bipolar chest lead (CV_5). A U wave is visible at the rate of 107 elevating the onset of P and apparently ending during the P wave. The P R slope is probably atrial repolarization. The exact position of the QRS in the T wave is uncertain but this is of little consequence since this slight degree of P R slope permits the use of the QRS onset as a reasonable base line for measurements of ST T.

At faster rates, however the T U and P conglomeration increases until at 154 a "T P" wave is formed. The P R slope is now more evident. How much of the apparent P elevation and P R sloping is definitely caused by a change in atrial electrical activity?

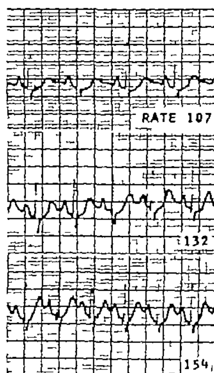


Fig 6. A single bipolar chest lead exercise electrocardiogram. Changes in the P wave and P R segment may be explained by wave summation.

The U amplitude at the rate of 107 measured from the P R segment level is approximately 1 2 mm. The P wave measured vertically from its sloping base, is about 2 6 mm. A slight increase in U amplitude and a decrease in the Q-U interval would be expected with cardiac acceleration.[7] At the rate of 154 synchrony of P and U peaks with no T contribution could cause an electrocardiographic deflection of 4 mm. These changes in P and P R may therefore be explained primarily by wave summation.

The T wave shortens and deepens in tachycardia[8] and it can become more evident even without alterations of the P wave but because of U wave summation the contribution of the T change to the P R slope in this illustration cannot be quantitated. Therefore T wave distortion of the S-T segment cannot be predicted and a base line is approximated by the QRS onset.

Those who would fit an arc to the P R and S-T segments[4] in order to estimate the course of atrial repolarization will find

the P-R and S-T segments in Fig. 6, rate 154, to be tempting. The apparent relationship in this example may be fortuitous.

Definite changes in this exercise series (Fig. 6) include slight alteration of Q/R/S ratios (probably related to a small shift in axis) and increased T amplitude. Decreased Q-T and Q-U intervals are very probable.

Summary

Electrocardiograms recorded during movement of the patient may be distorted by gradual and abrupt shifts in the base line. Both forms of artifact can be visually excluded by interpreting only those complexes that appear in superimposable pairs. Base-line horizontality is not essential for the accurate measurement of waves.

The overlap in time and consequent voltage summations of T, U, and P waves in tachycardia may cause misinterpretations of cardiac electrophysiology by obscuring the onsets and terminations of waves, by altering the position of wave apexes, and by producing distortions of amplitude. Wave summations alone may in some cases explain apparent P wave enlargement and T wave visualization.

P-R segment extrapolation techniques for S-T segment evaluation can be safely employed only with a knowledge of the undistorted P amplitude and duration and the components of the sloping P-R segment.

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Varying vectorcardiographic patterns in anomalous left coronary artery arising from pulmonary artery

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Myocardial infarction is a rare phenomenon in infancy, and when it occurs, the underlying malformation may be anomalous origin of the left coronary artery from the pulmonary artery (LCPA). Recent communications[1-4] have clarified the hemodynamics of the coronary circulation and discussed methods of surgical relief.[5-7]

Vectorcardiography is a recognized tool in the diagnosis of the site and extent of myocardial ischemia and infarction.[8-11] The vectorcardiographic findings in LCPA have been reported to be of diagnostic value.[12-14]

The present communication concerns chiefly the vectorcardiograms in 3 consecutive infants with LCPA who underwent surgical ligation of the anomalous vessel between 1963 and 1964. The recent vectorcardiographic findings in 2 older children who had undergone pericardial phenolization and poudrage in early infancy are also included.

Variations in vectorcardiographic patterns were observed which appear to be related to varying extents of myocardial infarction. This is in contrast to some of the previous reports[12-14] which have uniformly emphasized a single pattern of configuration of the QRS loop in the horizontal plane. Different outcomes of surgical interruption of LCPA appeared to be reflected in postoperative vectorcardiograms and seem to be related, among other things, to differing sizes of LCPA which carried the retrograde flow of blood.

Material and methods

The patients are divided into two groups (Table I). Group I includes the 3 patients who underwent ligation of LCPA, and in 2 of these both preoperative and postoperative vectorcardiograms were recorded. Group II includes 2 patients who underwent pericardial poudrage and phenolization in early infancy, and in whom preoperative and postoperative electrocardio-

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Table I. Clinical features and anatomic data

Patient	Sex race	Age (mo) at time of diagnosis	Important symptoms	Cardiac findings	Special studies	Surgery	Anatomy (Noted at surgery and/or necropsy)
Group I							
1. M.A. #1094689	M W	6	1. Labored breathing and diffuse perspiration on feeding 2. Episodes of vomiting not related to feeding 3. Hacking cough and wheezing respiration 4. Presented with acute cardiorespiratory distress	Massive cardiomegaly chiefly on left side; gallop rhythm short soft systolic murmur heart sounds poor in quality	Cinecatheterization with aortography	Attempted ligation of LCPA Died 1963	Massive infarction; marked dilatation, some hypertrophy endocardial and subendocardial sclerosis with focal areas of calcification in left ventricle some dilatation of right ventricle
2. L.G.M. #1109671	F C	5	Episode of pneumonia cary thing on feeding breathing difficulty	Left-sided cardiomegaly gallop rhythm no murmur	Cinecatheterization with aortography	Ligation of LCPA, 1964	Big collaterals large LCPA with retrograde flow; anterolateral infarct
3. D.P. #1045011	F C	21	Episodes of dyspnea cough lethargy	Left-sided cardiomegaly gallop rhythm heart sounds fair soft systolic murmur	Cinecatheterization with aortography	Ligation of LCPA 1964	Small LCPA (1 mm in diameter) with retrograde flow large RCA with good collaterals anterolateral infarct more anterior
Group II							
4. T.W. #937437	F C	3	Labored breathing and cough associated with feeding	Left-sided cardiomegaly poor heart sounds no murmur	Venous angiocardiography	Phenolization pericardial poudrage 1958	Anterolateral surface scarred and thin-walled Viable tissue on posterior wall and septum
5. A.B. #927601	F W	4	Crying, arching of head choking and cough during feeding dyspnea	Left-sided cardiomegaly; heart sounds fair no murmur	Venous angiocardiography	Phenolization pericardial poudrage, 1956	Anterolateral surface gray white and thin with poor contractility

W White C Colored (Negro)

grams and a recent vectorcardiogram were studied

The clinical profile is summarized in Table I All the infants appeared to be normal at birth and had an uneventful neonatal period Symptoms of varying severity appeared between the second and third months of life. The first difficulties were noted in association with feeding These varied from easy tiring coughing and labored breathing to frank spells of crying arching of head and drawing up of legs—interrupting the feeding process. Respiratory symptoms were prominent in all Presentation at the time of diagnosis consisted of gross cardiomegaly and decompensation on the left side. Heart sounds were often of poor quality and gallop rhythm was uniformly present. Only occasionally was a short soft systolic murmur heard In none of the cases was a murmur suggestive of mitral insufficiency heard The diagnosis was established at from 3 to 6 months of age in 4 patients, and at 22 months in 1 patient.

Cinecatheterization was used to establish the diagnosis in Group I The right coronary artery (RCA) was seen to be filling normally after injection of contrast material at the root of the aorta Subsequently the left coronary artery was filled in retrograde fashion followed by the appearance of the dye in the pulmonary artery This indicated the retrograde nature of the flow from right coronary artery to left coronary to pulmonary artery

Patient 1 died during induction of anesthesia and necropsy was performed He was found to have very extensive infarction of the left ventricle some hypertrophy of the posterobasal and septal regions, and subendocardial sclerosis with focal areas of calcification.

The other 2 patients underwent successful ligation of the left coronary artery near its origin from the pulmonary artery This vessel was found to be of good size in Patient 2 and was very diminutive in Patient 3 Although complete exploration of the myocardium was not made the impression was that the infarction was less extensive in these 2 patients than in Patient 1 and furthermore that it was less in Patient 2 than in Patient 3 There was functional improvement in the cardiac status of both of the patients. However whereas heart size decreased in Patient 2 it remained unchanged in Patient 3

In Group II the diagnosis was primarily clinical and venous angiography demonstrated immensely dilated thin walled left ventricles with poor contractility At the time of operation extensive infarction was noted in both The patients improved remarkably after surgery and have continued to do well for 7 to 8 years in spite of persistent cardiomegaly In these 2 patients the only vectorcardiograms recorded were those taken during a recent visit.

Vectorcardiograms were recorded using Grishman's[14] cube system of electrode placement, and oscilloscopic patterns were photographed with a Polaroid camera. Horizontal frontal and right sagittal views were recorded and the electronic beam was interrupted 400 times per second Electrocardiograms were recorded with a Sanborn twin-channel electrocardiograph using a paper speed of 25 mm per second

Results

Analysis of the vectorcardiograms revealed variations in the morphologic configuration in the horizontal projection abnormal orientation of the time vectors and slurring and anomalous conduction at some phase of the QRS vector loop

Group I Preoperative findings In the *horizontal plane* the morphologic configuration of the QRS loop was found to be variable. It was inscribed clockwise (CW) in Patient 1 (Fig 1 *Aii*) counterclockwise (C CW) in Patient 2 (Fig 2 *Aii*) and counterclockwise-clockwise in Patient 3 (Fig 3 *Aii*) In addition sharp angulations of the loop were seen in Patient 1 whereas in Patient 3 there was a medial bend on the centrifugal limb

Analysis of the time vectors also revealed differences 0 01 and 0 02-sec. vectors were directed anteriorly in the midline at about +90 degrees in each of the patients. In Patient 2 conduction delay was seen over this part of the vector loop (Fig 2) The 0 03-sec. vectors showed marked differences in orientation In Patient 1 this vector was inscribed clockwise to the right and anteriorly at ±180 degrees. In Patients 2 and 3 it was counterclockwise to the left,

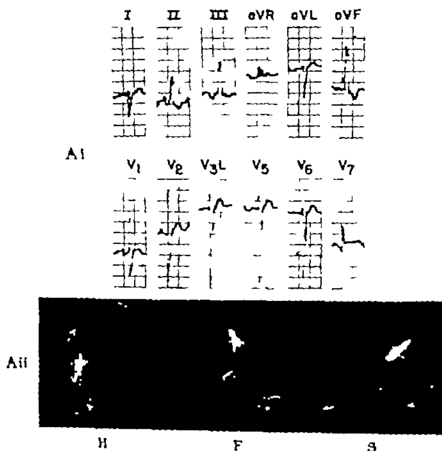


Fig. 1 Patient 1 (M.A.). *AI* ECG shows Q wave in Lead V R wave moderately tall in Leads V to V and V_7, small in Leads V to V_6. Slurring and widening of QRS complexes. *AII-H plane*, CW initial 0.03 sec anterior and to the right, body of QRS loop to left and posterior with plateau formation. *F plane* C-CW deformity of outgoing limb. *S plane* CW upward bending of the inferior limb T loop spatially opposed to QRS loop.

partly anterior (first 5 msec) and partly posterior In Patient 2 it constituted the maximum vector directed at −60 degrees

The 0 04-sec. vector was directed to the left and posteriorly at −60 degrees and constituted the maximum vector in Patients 1 and 3 The 0 05-sec vector in Patient 1 was characterized by a plateau like delay (Fig. 1) In Patient 3 0 05-sec and subsequent vectors showed conduction delay (Fig. 3)

In the *frontal plane* the direction of inscription was counterclockwise and the QRS loop was located inferiorly with the maximum vector between +65 and +85 degrees. The initial vectors were in the midline or to the right at +90 to +95 degrees. In Patient 3 (Fig 3) alone was the terminal 0.02 sec. oriented superiorly

There was an arc like deformity in the middle of the loop in Patient 1 correspond ing to the plateau-like delay seen in the horizontal plane (Fig 1)

In the *sagittal plane* the QRS loop was inscribed clockwise In general it con firmed the anteroposterior and superior-inferior dimensions of the vector loop as depicted in the other two planes.

Group I Changes after ligation of LCPA Patient 2 (Fig 2 *B* *C*) showed changes that reflected striking shrinkage in the area of infarction and ischemia whereas in Patient 3 (Fig 3 *B* *C*) there was evi dence initially of some increase in the area of lateral infarction which reversed sub sequently

In Patient 2 the QRS vector loop showed, postoperatively progressive widening of

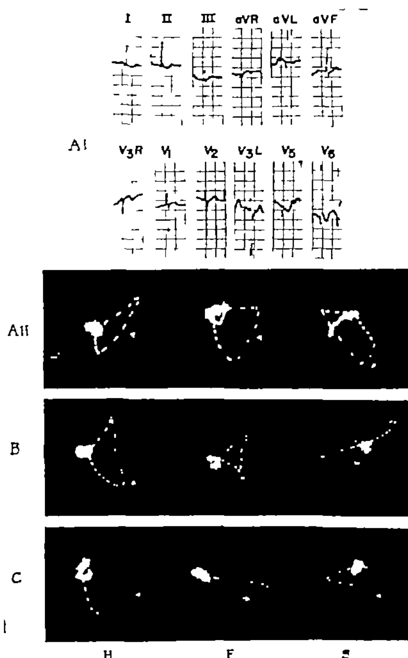


Fig. 2. Patient 2 (L.G.M.). *AI Preoperative ECG* shows Q in Leads I, aVL, V_6, and V [illegible] diminutive in Lead I. Deep S from Lead V_1 to Lead V_6. R small Lead V [illegible] to Lead V_6, tall in Leads V_1 and V_6. *AII-VCG H plane:* C-CW with looping and slurring of initial vectors. *F plane:* C-CW. *S plane:* CW. Initial 0.02 sec. anterior remaining 0.0 [illegible] sec. posterior. *B. Two weeks after ligation of LCPA. H plane:* widening of QRS loop. *F plane:* CW and superior location. *S plane:* C-CW, linear shape, placed above the E point. *C. Two months after surgery. H plane:* Wide QRS loop, disappearance of initial slowing. *F plane:* C-CW, placed transversely to the left. *S plane.* Placed anteroposterior below E point.

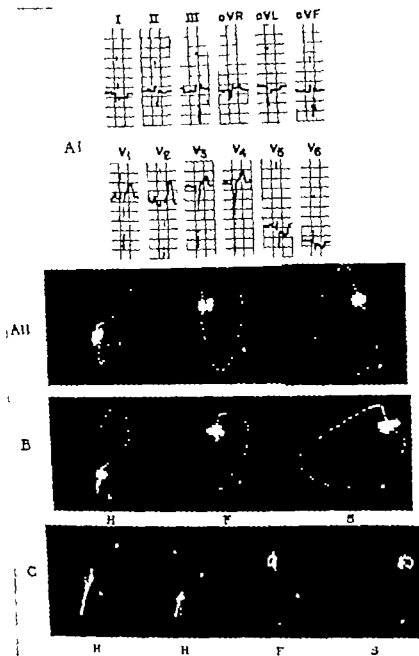


Fig. 3. Patient 3 (D.P.). *A I Preoperative ECG* shows Q waves in Leads I, aVL, V [illegible] and V [illegible], deepest in Lead aVL and diminutive in Leads V [illegible] and V [illegible]. Deep S from Lead V [illegible] to Lead V [illegible]. R moderate size in Leads V [illegible] and V [illegible], diminutive in Leads V [illegible] and V [illegible], and tall in Leads V [illegible] and V [illegible]. *A II VCG. H plane:* Figure-of-eight QRS loop with centrifugal limb C-CW and showing mild medial bend, centripetal limb CW with lateral bend and terminal delay. *F plane:* C-CW, terminal vectors superior. *B. Two months after ligation of LCPA. H plane:* Reversal of early portion of QRS loop from C-CW to CW. *C. Four months after surgery:* C-CW inscription of early vectors is restored.

the loop in the horizontal plane with a marked increase in the left anterior area Conduction delay that was seen preoperatively over the initial 0 02 sec disappeared by 2 months postoperatively The 0 02 sec. vector showed some leftward shift. The total QRS duration remained unchanged

In the frontal plane there was an initial rather abrupt change from a counterclockwise inferior loop to a clockwise and superior loop at 2 weeks postoperatively (Fig 2 *B*) Subsequently it reversed back to counterclockwise inscription was linear in shape and was placed transversely to the left with the maximum vector at +10 degrees (Fig 2 *C*) This leftward shift would also point toward improvement in left lateral forces

In the sagittal plane the vector loop was at first inscribed counterclockwise and was located obliquely superior whereas in the later stage it reversed to clockwise inscription and was transversely placed beneath the E point

The transient changes observed at 2 weeks would indicate temporary ischemic changes in the inferior wall

In Patient 3 a postoperative vectorcardiogram (Fig 3 *B*) at 2 months showed that the 0 02 sec. vector had shifted to the right from a midline anterior position The first 5 msec. were anterior and the later 5 msec were posterior and close to the midline leading to a clockwise inscription of the whole loop in the horizontal plane At 4 months this vector (Fig 3 *C*) had again moved to the left The major part of the loop remained essentially unchanged during this period Thus, in contrast to Patient 2 there was no evidence of actual decrease in the area of infarction

Group II The vectorcardiograms in these 2 patients (Figs. 4 and 5) were recorded 7 to 8 years after pericardial phenolization and poudrage. Both records suggest left ventricular hypertrophy and peri infarction block In the horizontal plane the vector loops were inscribed counterclockwise and manifested deform



Fig. 4 Patient 4 (T W). VCG seven years after pericardial phenolization. *H plane:* C-CW slowing and slurring of the afferent limb. *F plane:* C-CW terminal vectors superior *S plane:* CW initial vectors anterior major part posterior



Fig. 5 Patient 5 (V.B). Eight years after pericardial phenolization. *H plane* C-CW Initial 0 01-sec. deflection anterior remaining QRS loop posterior with multiple deformities, initial and terminal slowing *F plane* C-CW initial part inferior and later part superior *S plane.* CW

ities. The 0.01-sec. vector was directed anteriorly in the midline whereas the 0.02 sec. vector was partly anterior and partly posterior in Patient 4 and posterior in Patient 5 The maximum vector was directed at −60 degrees. The terminal vectors forming the returning limb showed conduction delay The loop was inscribed counterclockwise in the frontal plane and clockwise in the sagittal plane A variable part of the terminal vectors was oriented superiorly and showed conduction delay The initial and terminal vectors formed an angle of 180 degrees.

Electrocardiographic features The frontal plane axis lay between +55 and +105 degrees in 4 of the 5 patients and was +35 degrees in one (Table II) Leads I and aVL showed tall R waves with no S wave, except in Patient 1 who showed an rS pattern (Fig 1 A_1)

In the precordial leads V_1 showed a tall to medium-sized R wave with deep S wave. In leads farther to the left, the R wave either decreased or remained unchanged in size, whereas the S wave progressively increased in depth An abrupt change to a tall R wave pattern occurred in Leads V_5 and V_6, and in one patient in Lead V_7 (Fig 1 A_1)

The incidence of abnormal Q waves in different leads showed marked variation. The abnormal Q waves consistently showed an increase in duration to 0 03 to 0 04 second whereas the depth was quite variable, ranging from 1 to 18 mm in amplitude In Patient 1 a Q wave was observed only in Lead V_7 where it was 2 mm. deep (Fig 1 A_1) In the other patients the Q wave was deepest in Lead aVL, varying from 5 to 18 mm In Lead I it varied from 1 to 7 mm and in Leads V_5 and V_6 from 1 to 13 mm.

Slurring of the QRS complexes of varying degree was seen in all patients. It was particularly striking in 2 patients with widening of the QRS to 0.08 to 0.09 sec

The T wave was flat or inverted in leads on the left side in 4 patients, whereas in 1 patient it was inverted in Leads II III and aVF

Changes after surgery In Patient 2 at 2 months after ligation of LCPA, there was a decrease in the Q wave in leads on the left and an increase in R wave voltage in the mid-precordial leads and hence, reversal of the abnormal QRS transition seen preoperatively

Patient 3 showed no significant change in the electrocardiogram postoperatively

In Patients 4 and 5 although Q-wave abnormality decreased postoperatively abnormal QRS transition in the precordial

Table II Electrocardiographic findings

Patient	QRS axis	Limb leads (QRS pattern)		Precordial leads (QRS transition)					Abnormal Q wave (mm)
		I	II and III	V	V	V	V	V	
1 M.A.	+105	rS	qR	15/10	6/36	6/35	5/33	3/30	Only in V 2
2. L.G.M	+55	qR	Rs	5/14	5/23	—	1/0	25/0	I aVL, V, V 1 3 5 3
3. D.P	+35	qR	RS	12/25	1/30	6/35	33/8	23/3	I aVL, V, V 4 9 3 1
4 T.W	+60	qR	RS	5/17	5/35		1.5/12	17/0	I aVL, V 4 10 7
5 A.B.	+70	qR	RS	8/10	3/40		26/0	30/0	I aVL, V, V 7 18 13 13

leads persisted at 7 to 8 years after phenolization

Discussion

Clockwise direction of inscription of the QRS vector loop in the horizontal plane has been regarded to be the characteristic *feature of the vectorcardiogram in cases* of LCPA.[13,14] However as shown in this series the pattern of configuration varies. It may be clockwise partly counterclockwise and partly clockwise or entirely counterclockwise. It seems to us that this variation is determined by the severity and extent of infarction Thus Patient 1 with a clockwise loop in the horizontal plane, was found at autopsy to have very extensive infarction of the entire left ventricle with the exception of the interventricular septum By contrast Patient 2 with a counterclockwise loop was thought to have a more localized infarct at the time of surgery Patient 3 with a partly counterclockwise and partly clockwise loop appeared to fall somewhere between the other two patients with respect to the severity of infarction

Furthermore, the results of surgery would also appear to support this assumption. Whereas the patient with a clockwise loop died during the induction of anesthesia the one with a counterclockwise loop has undergone successful ligation of LCPA with postoperative vectorcardiograms indicating regression of the infarct pattern. Regression of heart size was seen on chest films LCPA was found to be of fair size in this patient and large collateral vessels were seen In the patient with a figure-of-eight loop (Fig 3) however LCPA was found to be diminutive in size and after ligation of it the postoperative vectorcardiograms showed no signs of improvement. This may be considered to be indirect evidence suggestive of a larger area of infarction in Patient 3 than in Patient 2.

Additional support comes from the cases of 2 children who had undergone pericardial poudrage in infancy The fact that they have survived up to this age would suggest that their residual infarction is not so extensive. Both of them showed a counterclockwise-inscribed QRS vector loop

It would appear to be reasonable therefore to assume that the general configuration of the QRS loop in the horizontal plane may serve as an index of the severity of the infarction and possibly have some prognostic significance Although a clockwise configuration would suggest a more *extensive infarction* and *portend a serious* prognosis, a counterclockwise loop would on the other hand indicate a more localized infarction with best prospects for regression in the area of infarction after surgery

Time vector analysis Changes in the orientation of the initial vectors were suggestive of the presence of infarction of the anterolateral wall of the left ventricle.[14] In this respect the 0 01 sec vector appeared to be normally oriented indicating relative integrity of the interventricular septum Rightward lagging of the 0 02-sec vector and of the 0 03-sec. vector in one patient, indicated a decrease in left lateral forces during this phase of ventricular activation Medial bending of the 0 03 and 0 04-sec vectors in Patient 3 would suggest a similar decrease in forces. Posterior displacement of these vectors when seen would be accounted for by dominance of posterior forces due either to a decrease in anterior forces resulting from anterior infarction or to an increase in posterior forces resulting from posterobasal hypertrophy or to a combination of both Such compensatory localized myocardial hypertrophy is described as a characteristic response observed in cases of LCPA[17]

In some instances the late vectors were superior in orientation and revealed conduction delay This would point to anomalous conduction

Intraventricular conduction defects Anomalies of intraventricular conduction with features reminiscent of peri infarction block[18] were seen in most of the patients. The angle between the initial and terminal vectors was 180 degrees in 3 patients whereas in the other 2 the initial and terminal vectors were opposed to each other in the sense of anterior/posterior and right/left while the angle between the two did not exceed 160 degrees. The site of conduction delay on the QRS loop also varied Although the characteristic delay of the terminal vectors was seen in

3 patients it was confined to initial vectors in one and to mid vectors in the others. Anomalies of intraventricular conduction have not been emphasized before.

Electrocardiographic abnormalities The electrocardiographic changes in this anomaly have been discussed frequently.[7,11,13] A feature of special interest to us has been the abnormal transition of the QRS complex across the precordium. Increased duration of the Q wave is considered to be more significant than its depth. Deep Q waves seen in left ventricular hypertrophy or even normally in infants are usually narrow and spiky whereas the Q wave described here is wide and often slurred.

Normal to near right axis seen in limb leads in the presence of evidence of left ventricular hypertrophy in the precordial leads is also of interest. Slurring of some part of QRS complex with or without obvious widening is considered to be a helpful sign. This is in contrast to the findings of Noren and associates,[13] who reported absence of abnormal conduction in their cases.

The fact that typical Q wave abnormality was not seen until Lead V_7 in at least one patient suggests that leads further to the left of V_6 should also be recorded. Of all leads, the Q wave was found to be most prominent in aVL.

Postoperatively regression of the infarct pattern was indicated by a decrease in the Q wave and a restoration of the normal QRS transition in the precordial leads.

"Electrical silence" versus biological death of the myocardium The rather rapid reversal of vectorcardiographic changes of anterolateral infarction and the transient changes suggestive of inferior wall infarction observed in Patient 2 raise the important question of electrically silent areas being distinct from biologically dead areas of myocardium.[18] Although biologically dead tissue is not likely to regenerate, the electrically silent areas could be revitalized on restoration of adequate local circulation. Since mechanical contraction depends essentially on electrical excitation, myocardial function would be expected to improve after electrical restoration. We believe that electrically silent areas were considerably more extensive than anatomically dead myocardium in most patients in this series. The restoration of those areas would account for the postoperative electro-vectorcardiographic evolution of the infarct pattern. Furthermore this would seem to explain the improvement that took place in spite of persistent cardiomegaly in Patients 3, 4, and 5.

Summary

Five patients with LCPA (anomalous origin of the left coronary artery from the pulmonary artery) were studied. Three of them underwent ligation of the anomalous vessel (Group I) whereas 2 had undergone pericardial phenolization some years previously (Group II).

In the preoperative vectorcardiograms, morphologic configuration of the QRS vector loop in the horizontal plane was found to be variable. Clockwise inscription was found to be related to a very extensive infarction of the left ventricle. Counterclockwise inscription, on the other hand, was found in a patient with a more localized area of infarction which showed quick regression after ligation of LCPA. The patient with a loop inscribed partly counterclockwise and partly clockwise appeared to fall into an intermediate position with respect to area of infarction. It is suggested that this spectrum of morphologic configuration may serve to indicate the severity of infarction and the general outlook.

Time vector analysis was found to provide useful information.

After ligation of LCPA in one patient changes indicative of regression of infarction appeared: widening of the QRS loop to the left and anteriorly in the horizontal plane and leftward shift of the mean axis in the frontal plane.

Evidence of intraventricular conduction defect with features suggestive of peri-infarction block was seen.

On the electrocardiogram the features of interest were abnormal QRS transition in the precordial leads, varying distribution of abnormal Q waves, and slurring of QRS complexes with or without widening.

Vectorcardiographic analyses were found to be useful in evaluating the severity and extent of infarction and as a guide to its regression after surgery.

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Aortic regurgitation in the elderly

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This investigation was undertaken in order to determine the incidence and insofar as possible the etiology of aortic valvular insufficiency in an elderly medical population. The stimulus for this study was the observation that aortic insufficiency of uncertain cause was frequently encountered in elderly patients in this institution.

Methods

Three hundred and nine patients who were 65 years of age or older were examined. They represent consecutive admissions in this age group to the medical services of the District of Columbia General Hospital. Two hundred and ninety-one patients, of whom 81 per cent were Negro, were the subject of this study. Eighteen patients were excluded because death or discharge occurred before two of the participating physicians had examined the patient. Two of the 18 patients excluded were thought to have aortic incompetence either by the ward physicians or by one of the authors.

The District of Columbia General Hospital serves the indigent residents of the District. All but a few patients were admitted to the medical service from the emergency room with acute illnesses or exacerbations of chronic disease. Patients were not admitted for chronic care.

With few exceptions, the patients were interviewed first and then examined by one of us (A.B.) within 24 hours of admission. The interview consisted of a series of questions designed to elicit a history of the more commonly recognized etiologies of aortic insufficiency, including rheumatic fever, rheumatoid arthritis, ankylosing spondylitis, syphilis, hypertension, bacterial endocarditis, dissecting aneurysm of the aorta, and chest trauma. The first examining physician recorded whether the history was suggestive or convincing of these disorders. Then, prior to auscultation of the heart, the systolic and diastolic blood pressures were recorded, whether aortic insufficiency was or was not present. All patients were examined for deformities of the joints consistent with ankylosing spondylitis and rheumatoid arthritis. Auscultation to determine the presence of aortic regurgitation was performed by listening with the flat diaphragm of a

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Rappaport Sprague stethoscope along both the left and right sternal borders, as well as at the apex If the patient could sit upright this was the preferred position for examination The intensity of the systolic and diastolic murmurs was graded on a scale of 1 to 6

The only information given the second and third observers was the name and location of the patient The second observer F M used a Harvey Cefaly stethoscope Auscultation was performed as described previously Several different physicians constituted the third observer They were in their second to fourth year of post graduate training in internal medicine. In addition the patients were examined by fourth year medical students and the ward physicians. When a difference of opinion existed in regard to the presence of aortic regurgitation a second auscultation was carried out by the three observers. If a difference of opinion still existed the physician who heard the murmur would demonstrate it to the other observers. With regard to the first two observers, this occurred on three occasions By these means, there was no instance of lack of agreement among the first two observers as to the presence or absence of aortic incompetence

In those patients with diagnostic murmurs further history physical examination and laboratory tests were obtained in an attempt to determine the etiology of aortic regurgitation The records of the present admission as well as of previous admissions, were reviewed In addition the first observer re-examined the patient to determine the presence of some of the more unusual causes of aortic incompetence such as Marfan s syndrome[1,2] lupus erythematosus,[3] and osteogenesis imperfecta[4] Blood pressures were recorded in all four extremities to detect differences suggestive of dissection of the aorta Auscultation of the heart was repeated to determine any associated valvular lesions

In all patients with aortic insufficiency a hematocrit electrocardiogram and posterior anterior chest roentgenogram were obtained When possible chest roentgenograms in the lateral and both oblique projections were recorded A Venereal Disease Research Laboratories slide-flocculation test (VDRL) was done in all except 2 of the patients with aortic incompetence. If the VDRL test was reported to be reactive a Kolmer Reiter protein complement fixation test (KRPCF) was performed If both of these tests were reactive, it was accepted as sufficient evidence of syphilis, past or present[5] If the VDRL was reported to be nonreactive or weakly reactive a *Treponema pallidum* immobilization test (TPI) was performed by the Venereal Disease Research Laboratory Division of the United States Public Health Service in Chamblee, Georgia There were no instances of a strongly reactive VDRL and nonreactive KRPCF VDRL tests were also obtained on the last 100 patients studied who did not have aortic regurgitation Roentgenograms of the spine were taken in those patients in whom the diagnosis of ankylosing spondylitis was suggested by history or physical examination

Patients with aortic insufficiency were re-examined every few days during their hospitalization with specific attention to the effect of improvement of anemia hypertension or congestive heart failure on the intensity of the murmur

Eight of the patients with aortic incompetence died during the period of observation. Autopsies were performed in 2 cases.

Results

Thirty four (12 per cent) of the 291 patients studied had a diastolic murmur typical of aortic insufficiency Although angiocardiography or cardiac catheterization was not performed to prove the presence of aortic regurgitation the diagnosis was established with assurance since the murmur had the high pitched decrescendo quality characteristic of aortic insufficiency and started immediately after the second heart sound With regard to other possible causes of the diastolic murmur insufficiency of the pulmonary valve was not considered to be likely in our patients for the following reasons. The murmur of idiopathic pulmonary valve insufficiency has a lower pitch and usually occurs in mid diastole.[6,7] The murmurs heard were thought not to represent pulmonary insufficiency secondary to pulmonary hypertension since there was no clinical elec

Table I. The incidence of syphilis in patients with aortic insufficiency

Serologic tests	Number of patients
A. Evidence of past or present syphilis	
VDRL* strongly reactive KRPCF† reactive	12
VDRL weakly reactive TPI‡ reactive	6
VDRL nonreactive TPI reactive	5
Total	23
B. Absence of infection with syphilis VDRL nonreactive TPI nonreactive	9
C. No serologic tests performed	2

*Venereal Disease Research Laboratories slide-flocculation test.
†Kolmer Reiter protein complement fixation test.
‡*Treponema pallidum* immobilization test.

trocardiographic or roentgenographic evidence of pulmonary hypertension. In no patient was there an impression of a continuous murmur. Therefore it is considered that the diastolic murmur heard represented insufficiency of the aortic valve.

There was serologic evidence of syphilis in 72 per cent (23 of 32) of the patients with aortic insufficiency. A positive VDRL was found in 56 per cent (18 of 32)* of the patients with aortic insufficiency as compared with 21 of the last 100 patients examined who did not have aortic incompetence (Table I). This difference appears to be significant since the patients with aortic insufficiency and the control group were, in other respects, comparable. The incidence of reactive VDRL tests in the patients with the aortic diastolic murmur was relatively constant throughout the study, being 45 per cent in the first 11 patients with aortic insufficiency, 55 per cent in the next 11, and 58 per cent in the last 12 patients with the murmur.

Diastolic hypertension of a degree sufficient to be solely responsible for aortic insufficiency was, with few exceptions, not present in the patients with this murmur (Fig. 1).[9,10] Since aortic incompetence alleged to be associated with hypertension is of little hemodynamic significance, an appreciable decrease in diastolic blood pressure would not be anticipated.[9,11] Figs. 1 and 2 illustrate that the frequency distribution of the blood pressure readings in the patients with aortic insufficiency is similar to that in those without.

Attention was given to the presence and severity of anemia as a cause of aortic insufficiency. Seven of 34 (21 per cent) of the patients with the regurgitant murmur had a hematocrit on admission of 20 to 30 per cent. None were found who were more severely anemic. In no case did the murmur disappear despite partial or complete correction of the anemia, as has been shown by others.[12,13]

The murmur of aortic incompetence has been observed to be present when a patient is in congestive heart failure and to disappear with cardiac compensation.[14] Fifteen (44 per cent) of 34 patients with aortic insufficiency had congestive failure on admission. Improvement and/or apparent cardiac compensation did not result in disappearance of the murmur in any case.

More than one possible etiological factor to account for aortic insufficiency was frequently present. Therefore, it is difficult to be certain of the cause of aortic regurgitation in each individual. The various factors that may have been responsible for aortic insufficiency and the frequency with which they occurred are listed in Table II.

On the basis of history, physical examination, and laboratory tests as indicated, it was concluded that none of the patients with aortic insufficiency had lupus erythematosus, ankylosing spondylitis, scleroderma, bacterial endocarditis, Marfan's syndrome, osteogenesis imperfecta, significant chest trauma, dissecting aneurysm of the aorta, or Reiter's syndrome.

Although it was thought that the history obtained from the patients prior to examination might aid in determining frequently occurring etiological factors, there was no significant difference between the history obtained from the patients with aortic incompetence and that obtained from the control group, as illustrated in Table III. The absence of a marked difference between the two groups was not unexpected,

*In 2 patients with aortic regurgitation, serologic tests for syphilis were not performed.

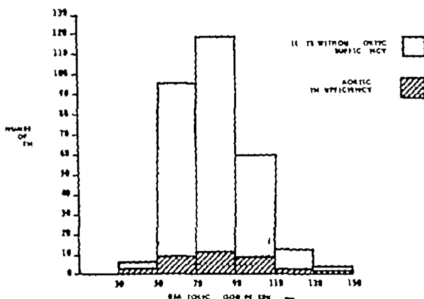


Fig. 1. A comparison of diastolic blood pressure in patients with and without aortic insufficiency.

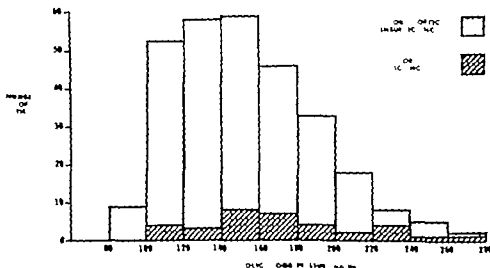


Fig. 2. A comparison of systolic blood pressure in patients with and without aortic insufficiency.

since the history was not dependable in the majority of patients. Indeed the history was completely unreliable because of disorientation in 26 per cent of the patients with aortic insufficiency and in 28 per cent who did not have the murmur.

Discussion

The stimulus for initiating this study was the impression that aortic insufficiency is a frequent occurrence in the elderly population at the District of Columbia General Hospital. This observation was verified since a diagnostic murmur was present in 12 per cent of our group.

The high incidence of seropositivity in the patients with aortic regurgitation indicates that syphilis was probably the cause of or contributed to aortic incompetence in many of these elderly patients.

Roentgenographic evidence compatible with syphilitic aortitis was present in 4

Table II *Possible causes or factors contributing to aortic insufficiency in 34 patients*

Causes or factors	*Number of patients*
Syphilis	23
Hypertension	11
Rheumatic heart disease	
Definite	2
Possible	3
Congestive heart failure	15
Anemia	7
Rheumatoid arthritis	1
Calcification of aortic valve of undetermined etiology	3
Perforation rupture or eversion of aortic cusps, of unknown cause†	1
None of the above-mentioned etiologies	4

Diastolic blood pressure more than 90 mm. Hg

†The musical quality of the diastolic murmur associated with its diastolic thrill was consistent with the pathology mentioned.[19] There was no evidence of an associated heritable disorder of connective tissue which might cause perforation of the aortic valve.[19]

Table III *Information obtained from history*

	Aortic insufficiency		*Control group*	
	Number	*Per cent**	*Number*	*Per cent**
History suggestive of rheumatic fever	2	8	8	4
History of hypertension	11	44	72	39
History of syphilis	4	16	20	11

*Per cent of patients who were questioned and judged to be able to answer questions.

patients. However there were 19 patients with the aortic diastolic murmur who had serologic evidence of syphilis but no roentgenographic evidence characteristic of syphilitic aortitis. Autopsies were performed on 2 patients in this latter category. Clinical summaries and pathologic reports on these 2 patients illustrate the difficulties in determining the etiology of aortic insufficiency on the basis of either clinical or pathologic findings.

Case 1 J.G a 72-year-old man was admitted to the District of Columbia General Hospital with a chief complaint of chest pain and dyspnea. In 1958 he had had a transient hemiplegia of the left side. At that time, a Grade 1/6 diastolic blowing murmur was heard along the left sternal border. The blood pressure was 230/100 mm. Hg. He recalled having been treated for syphilis. The serum VDRL and KRPCF were reactive. Cerebrospinal fluid VDRL was nonreactive. When examined during the present admission he had a blood pressure of 150/80 mm. Hg. The previously described murmur was Grade 2/6. Autopsy confirmed the clinical diagnoses of old and recent myocardial infarction. No abnormalities of the aortic valve were detected. The characteristic gross pathologic changes of syphilitic aortitis were absent. Microscopic examination of the aorta showed round cell infiltration in relation to the vasa vasorum. The elastic lamellae were well preserved, and only minimal scarring was seen. It was the opinion of the pathologist that nonspecific aortitis was present.

Case 2 E.I a 72-year-old woman was hospitalized because of recurrent congestive heart failure. A Grade 3/6 diastolic blowing murmur as well as a Grade 3/6 systolic ejection murmur at the fourth left intercostal space, had been noted for 1 year during previous hospital admissions. At the time of the present admission, the murmurs were unchanged. The blood pressure was 200/60 mm. Hg. There was no history of syphilis or rheumatic fever. A serum VDRL was nonreactive, but a TPI was reactive. At autopsy there was calcification at the base of the aortic valve, with some fusion of the base of the noncoronary cusp and left coronary cusp. There was no evidence of rheumatic involvement of the other valves. There was neither gross nor microscopic evidence of syphilitic aortitis.

It will be noted in Table II that contributory factors could not be identified in 4 patients who are thus classified as having aortic incompetence of unknown etiology an incidence of only 1 4 per cent of admissions in this age group. However in the patients studied it is conclusive that hypertension, anemia and congestive heart failure are not important etiological factors. Therefore it may be more desirable to group patients with these conditions (excluding syphilis) as having aortic insufficiency of unknown etiology thus, 9 or 3 1 per cent of the patients examined had idiopathic aortic regurgitation. This latter classification was used by Bedford and Caird[11] who found an incidence of idiopathic aortic incompetence of 4 4 per cent of 3 142 admissions to a geriatric unit in Oxford England These investigators did

*We are indebted to Dr. William C. Manion, Chief of the Cardiovascular Branch of the Armed Forces Institute of Pathology, for reviewing the microscopic sections.

not routinely perform the TPI test when the Wassermann and Kahn tests were non reactive. If the same criteria of exclusion of syphilitic aortic incompetence were applied in the present study, 14 patients, or 4.8 per cent of admissions, would be listed as having idiopathic aortic regurgitation. This incidence determined in an indigent, predominantly Negro population in the United States is remarkably similar to that found by Bedford and Caird.[15] The latter authors stated that isolated aortic incompetence is as common as aortic stenosis in the elderly, as common as *all* forms of rheumatic heart disease combined and four times more common than syphilitic incompetence in old men and ten times more common in women. It is obvious that the population studied by Bedford and Caird had a considerably lower incidence of syphilitic aortic regurgitation, being 0.43 per cent of female and 1.01 per cent of male admissions, as compared with an incidence of 6.2 per cent in our series using the same diagnostic criteria. The incidence in the present study is 7.9 per cent if the diagnosis encompasses a nonreactive VDRL and a reactive TPI test.

An excellent and complete discussion of possible etiologies of idiopathic aortic valve insufficiency is given in Bedford's monograph.[3] Since aortic insufficiency appears to be common in the elderly, it is reasonable to attribute the etiology to some process of aging, either of the aortic valve or of its supporting structures, the aortic ring and the ascending aorta. The aortic valve undergoes an aging process in all layers.[1] Atherosclerosis of the valve cusp, beginning at the base of the cusp and extending along the edges toward the center, is seen after the fourth decade.[16] In addition to the pathologic changes which result in thickening of the valve cusps in older age groups, there are biochemical abnormalities which include an increase in acid mucopolysaccharide with age.[16] However, there is not sufficient evidence that the aging process affecting the aortic valve is sufficient to result in valvular incompetence. It is probable that dilatation of the aortic ring and ascending aorta, due to age and accentuated by disease involving the aorta, is responsible.

That there is an increase in the diameter of the ascending aorta with age has been clearly documented.[17,18] This is presumably due to degeneration and alteration of the elastic tissue in the media.[19,20] There is an associated functional decrease in the elasticity of the aorta with age.[21]

The aortic insufficiency found in this study was seldom hemodynamically significant, as demonstrated by the observation that the blood pressure was generally the same in patients with or without insufficiency (Figs. 1 and 2). Only 3 patients with aortic regurgitation had diastolic pressures that were less than 50 mm. Hg. In addition, the majority of the individuals with aortic insufficiency had diastolic murmurs that were only Grade 1/6 or 2/6.

Since the murmur was usually faint, the expectation would be that it would occasionally be undetected by the examining physicians. It was not expected, however, that the murmur would be missed by the ward physicians in 53 per cent of patients with aortic incompetence. Although it has been recognized that the faint diastolic blowing murmur is frequently overlooked, the extent of this error has not, to our knowledge, been previously documented. The ability to detect the murmur of aortic insufficiency correlates well with the amount of training and/or experience of the examining physician (Table IV). The different stethoscopes used by the first two examiners were not responsible for error, since the murmur, once demonstrated, was as readily heard with either of the stethoscopes used. Other factors difficult to analyze may be partially responsible for failure to detect aortic incompetence. The first and second observers made certain that auscultation was performed under the most favorable circumstances possible. If auscultation under quiet conditions could not be achieved, examination was postponed. On several occasions, *rales due to pneumonia or congestive failure* prevented adequate auscultation. After appropriate therapy, the diastolic blowing murmur was readily heard.

Our observations are in agreement with those of Gouley and Sickel[22] that the murmur of aortic insufficiency in the elderly is frequently localized to a small area on the chest wall. It is usually best heard at

Table IV. The detection of the murmur of aortic insufficiency by several observers

Examining physician	Status of training	Murmur not detected in patients with aortic insufficiency: Number	Per cent
No. 2 (F.M.)*	Board Certified in Cardiology	1	3
No. 1 (A.B.)	Fellow in Cardiology	7	21
No. 3	Second-year to fourth year postgraduate training in internal medicine	12	35
Ward physicians	Predominantly first year and second-year postgraduate training in internal medicine; also fourth-year medical students	18	53

*Initials of examining physicians.

the lower left sternal border but occasionally may be localized at the apex or along the right sternal border.[22] In one of our patients with pulmonary emphysema the murmur was heard only in the subxyphoid area. In emaciated individuals the retraction of skin between the ribs prevented adequate contact of the diaphragm of the stethoscope with the chest wall. It then became necessary to apply the small bell firmly between the ribs. On the basis of the present experience it may be emphasized that detection of aortic insufficiency in the elderly must be done in a quiet room since the murmur is apt to be faint and localized to a small area on the chest wall occasionally in an atypical location.

The detection of aortic insufficiency of undetermined cause should alert the physician to the possibility of cardiovascular syphilis, even though it is recognized that syphilis is less common in an elderly population other than that seen in charity hospitals. Nevertheless, it is suggested that serologic tests to establish the presence of syphilis be obtained in every patient with aortic insufficiency in whom the etiology is not apparent. Since a nonreactive VDRL does not exclude cardiovascular syphilis, especially in the elderly, the TPI test should be performed under these circumstances.[14-21]

The presence of the diastolic blowing murmur of aortic insufficiency is of more than academic interest. Since the basic cause of the aortic regurgitation is often impossible to establish, and a rheumatic etiology cannot be excluded, antibiotic prophylaxis to prevent subacute bacterial endocarditis prior to dental manipulation or operative procedures should be recommended.

Summary

The incidence of aortic insufficiency was determined in 291 patients over the age of 65 who were admitted consecutively to the medical services of the District of Columbia General Hospital. The subjects were examined independently by three physicians for the presence of a diastolic blowing murmur. Twelve per cent of the patients had a murmur characteristic of aortic insufficiency. Other causes of a diastolic blowing murmur were excluded clinically.

Syphilis appeared to be a major cause of aortic regurgitation, since serologic evidence to substantiate this diagnosis was found in 72 per cent (23 of 32) of the patients with aortic incompetence. In this age group 7.9 per cent of the patients admitted to this hospital had aortic regurgitation associated with syphilis. These data suggest that syphilis may be a common contributing cause of incompetence of the aortic valve in such a patient population as that on which our study was based. The pathogenesis of aortic incompetence in those patients with syphilis who did not have characteristic chest roentgenographic evidence of the disease may be a minimal aortitis which accentuates the normal aging process of aortic dilatation.

Of patients examined 3.1 per cent had idiopathic aortic regurgitation. Treatment of anemia, congestive heart failure, or hypertension did not result in disappearance of the murmur.

The murmur was undetected by the ward physicians in 53 per cent of the patients with aortic insufficiency Although it has been recognized that the faint diastolic blowing murmur is frequently overlooked this is the first time that the extent of this error has been documented

It is recommended that, when the murmur is found antibiotic prophylaxis for bacterial endocarditis be instituted

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Experimental and laboratory reports

The musculovenous pumps of the human lower limb

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There is a good deal known of many aspects of the muscle pumps in the human lower limb The calf muscle pump was first studied and has most often been studied by measuring the effect of muscular exercise in the erect posture on the pressure in the superficial veins of the leg In small numbers of subjects the pressure within the posterior tibial vein on exercise has been measured Anatomic dissection measurement of venous pressure, and phlebographic studies of the lower limb during exercise have led to the concept of the calf as a reciprocating valved pump whose pump chamber consists of those veins enclosed within the deep fascia There are recent reviews which summarize this information.[8,11,13]

However most of this knowledge has been gained for the rather specific purpose of explaining the causes, and results, of disorders, such as varicose veins. Little attention has been paid to considering what function the muscle pumps may subserve in normal daily life. The anatomic features of the deep veins, especially those of the calf and the fact that their diameter is often quite disproportionately large in relation to the volume of blood flowing through them suggests that they have a specialized function.

The pressure is lowered in deep as well as in superficial veins by the action of the calf pump There is thus a considerable increase in the perfusion pressure of the calf muscles and thus may selectively increase the flow of blood in muscles which are used for ambulation.[11]

A second possible function of the leg veins is to act as a reservoir for blood its size being determined by venous tone. However evidence has been adduced which suggests that changes in venous tone do not greatly alter the volume of blood in the lower limb [14]

If venous *pressure* in the lower limbs is reduced by exercise, it follows that venous *volume* is also reduced It has been suggested that this is no more than a mechanism for permitting the dilatation of resistance vessels within the rather inelastic fascial envelope of the calf muscles—that is the gain of blood volume by arterioles and capillaries exactly counterbalances the loss from venules and veins.[19]

We have set out to examine in more detail two aspects of venous function in the lower limbs—the driving force of the muscle pumps in the leg and thigh and the actual changes in volume which occur at these sites during exercise.

Method

The subjects used in this study were normal males, 22 to 35 years old who had no evidence of abnormality of the veins of the lower limbs. The investigations were carried out in a room in which the

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temperature was kept at 20-22°C. Many aspects of the techniques have been described previously.[11-14]

1. *Measurements of muscle pressure.* A 0.5 mm. O.D. catheter was introduced percutaneously into the muscles selected for study. Pressure was recorded using a critically damped strain-gauge pen recorder system. In order to avoid blockage of the tip of the catheter it was necessary to introduce about 0.5 ml. of fluid into the muscle before each sequence of recordings. This remained effective for several minutes at a time. The fluid used was a mixture of saline heparin and lidocaine. This successfully prevented clotting in the catheter and rendered the subject completely free of pain during exercise.

In each muscle serial records were taken with the subject standing with the muscle completely relaxed, standing with the body weight equally distributed between the two limbs, undertaking a brief maximal isometric contraction of the muscle, undertaking a sustained isometric contraction of the muscle, reverting to standing with the muscle completely relaxed. The tension developed in the flexor muscles of the ankle could be approximately assessed by means of a weighing scale. Any record in which the pressure did not immediately fall to the resting level after contraction was discarded.

2. *Measurements of volume.* These were made with inflatable air plethysmographs,[13] which have the merit of permitting extremes of postural change or of muscular exercise with a minimum of artefact. Subjects were selected to have lower limbs of suitable contour so that a 10-cm. long plethysmograph could be fitted to the middle third of the calf and another 15-cm. long to the middle third of the thigh without slipping.

Blood flow in the calf was measured with the subject in the recumbent posture by conventional venous occlusion plethysmography, with an arterial occlusion cuff below the plethysmograph and a venous occlusion cuff at the knee. The latter could also be used as an arterial tourniquet. Blood flow in the thigh segment could not be measured so accurately because of the technical difficulty of positioning a venous occlusion cuff. An approximate estimate was obtained by producing occlusion of the common femoral vein by local pressure. This maneuver was also used in the upright posture to prevent the reflux of blood from the iliac veins. The absolute volumes in the thigh and calf segments were calculated from measurements of their circumference at three points; preliminary work comparing this technique with direct measurement of volume showed it to be accurate.

Initially each trained subject lay recumbent with the lower limb elevated 15 degrees while measurements of blood flow were made and until the volume in the limb segment became constant. He then stood rapidly upright without using the muscles of the leg under study. In the upright posture, he bore the body weight equally on the two limbs, until the volume in the limb segment reached a new steady level. This postural maneuver was repeated with simultaneous arterial occlusion at the knee, or occlusion of the femoral vein at the groin.

The effects of single maximal contractions of the thigh or calf musculature were measured separately, then the effects of rhythmic contraction-relaxation of the calf and thigh musculature separately, and finally the effect of cyclical contraction-relaxation of both thigh and calf.

In some subjects the changes in pressure in the great saphenous vein at the ankle were measured during these procedures.

Results

1. *Measurements of intramuscular pressure (Table I, Fig. 1).* Two subjects of average build were used and measurements of pressure were made in each muscle on two separate occasions. As may be seen from Table I, the range of values obtained for each muscle under resting conditions was quite small. The pressure with the muscle relaxed, or during quiet standing, was reproducible to within 1 or 2 mm. Hg throughout the 15 to 20-minute period of observation for each muscle. The pressure attained on maximal contraction of the muscle was also reproducible during the period of observation (cf. Fig. 1).

2. *Measurements of volume (Table II, Figs. 2, 3, 4).* Four subjects were used who were

Table I Intramuscular pressures (mm Hg) in the lower limb Average values from two subjects tested on two separate occasions

Muscle	*State of muscle*			
	Relaxed	*Quiet standing*	*Maximal contraction (single)*	*Maximal contraction (sustained)*
Vastus lateralis	9 (8-10)	16 (15-18)	140	115
Gastrocnemius-Medial head	9 (8-10)	22 (18-23)	230*	215
Soleus	15 (14-17)	48 (40-55)	250	250
Adductor	7 (6-8)	12 (11 15)	60	55

*Ankle flexor tension approximately 60 kilograms.

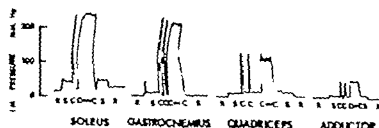


Fig. 1 Intramuscular pressures in the lower limb of a normal subject in the erect posture. Recorded by catheter in the *soleus* muscle, medial head of *gastrocnemius*, vastus lateralis (*quadriceps*) and *adductor* longus. *R.* Muscle relaxed. *S.* Quiet standing. *C.* Single maximal contraction. *C-C.* Sustained maximal contraction.

trained in the rather gymnastic technique required

There were rather striking differences between thigh and calf with regard to the filling curves when the upright posture was assumed (Figs. 2 and 3). After the movement artefact, the calf volume increased slowly and initially in an almost linear fashion. This rate was very similar to the rate of arterial inflow measured in the recumbent posture. It was unaffected by the application of a venous occlusion cuff at the knee immediately prior to standing. When a proximal arterial tourniquet was applied for 10 minutes, and released during the process of standing, the rate of filling was much increased although the final volume was unchanged. In brief the increase in calf volume seemed to be entirely dependent on arterial inflow.

The rate of filling of the thigh with the subject standing up was very much faster than in the calf and much faster than the apparent rate of arterial inflow with the subject in the recumbent posture. It was unaffected by an arterial tourniquet applied at the knee. When the femoral vein was occluded at the groin during the process of standing (although this was technically very difficult to achieve satisfactorily) the rate of filling was much less. This finding which was reproducible seemed also to largely eliminate artefact as an explanation of the apparent rapid initial filling. After the application of an arterial tourniquet at the groin for 10 minutes the rate of filling of the thigh was even greater although the final volume was unchanged

Table II Changes in volume (ml.) in segments of the calf and thigh. Average results in four normal subjects

	Thigh segment	*Calf segment*
Total volume—recumbent	2 860	925
Increase in volume from recumbent to standing	141	40
Reduction in volume in standing posture with		
Single maximal contraction of thigh or calf	31	23
Rhythmic thigh contraction—relaxation	22	17
Rhythmic calf contraction—relaxation	9	24
Cyclical contraction—relaxation of thigh and calf	23	26

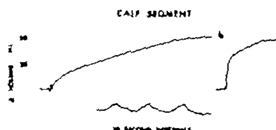


Fig. 2 Changes in volume in a 10-cm. segment of the calf. *a*, With change in posture from recumbent to quiet standing. *b*, As in *a* but with 10 minutes preceding application of an arterial tourniquet. *c*, Inflow curves after venous occlusion in the recumbent posture.

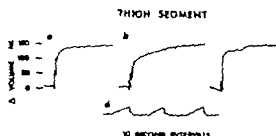


Fig. 3 Changes in volume in 15-cm. segment of the thigh. *a*, With change in posture from recumbent to quiet standing. *b*, As in *a* but with simultaneous local compression of femoral vein at groin. *c*, As in *a* but with 10 minutes preceding application of an arterial tourniquet. *d*, Inflow curves after occlusion of the femoral vein at the groin in the recumbent posture.

The findings were qualitatively the same in all 4 subjects. In other words, it appears that the thigh fills with blood initially by reflux from above rather than solely by arterial inflow.

The changes in volume which occurred in calf and thigh on exercise in the standing posture are displayed in Table II and Fig. 4. When contraction-relaxation of the thigh muscles alone was attempted, there was also a very substantial fall in calf volume and in the pressure in the great saphenous vein at the ankle. When exercise was confined to the calf, there was a small fall in thigh volume. It was very difficult, however, to confine exercise entirely to either calf or thigh. The rate of return of volume to the resting level gives some indication of the effect of the preceding exercise on arterial inflow in each segment.

During vigorous cyclical activity of both calf and thigh, about 15 per cent of the blood which had entered the thigh was expelled, and about 65 per cent of that which had entered the calf.

Discussion

1. Intramuscular pressures. The method used can be criticized as an absolute and very accurate measure of intramuscular pressure at rest, because it involves injecting fluid into the muscle.[17] However, after each fresh injection the pressure rapidly fell to a level which was reproducible over the 15 to 20-minute period of observation. The pressures measured during muscle contraction are less open to gross error from this source, and it is difficult to perceive how any possible valve action at the tip of the catheter could result in an overestimate of maximum pressure.

Only rather sporadic measurements of intramuscular pressure in man appear to have been made. Barcroft and Dornhorst[4] showed that the calf muscles could eject

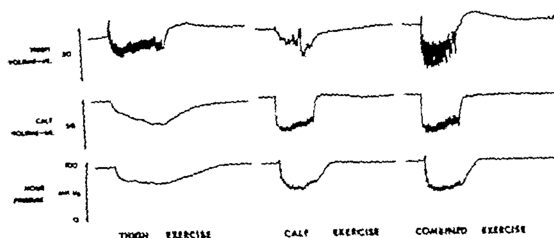


Fig. 4. Changes in volume in segments of calf and thigh in the erect posture during exercise of the *thigh* muscles alone, *calf* muscles alone, and *combined* exercise of calf and thigh, together with a trace of pressure in the great saphenous vein at the ankle.

Table III. Reported values of intramuscular pressure in the human lower limb

Author	*Muscle*	*Pressure at rest (mm. Hg)*	*Maximum pressure on contraction (mm. Hg)*
Henderson et al.[10]	Gastrocnemius	11	23
Hellebrandt et al.	Gastrocnemius	19*	30*
Wells et al.[8]	Soleus	13	87
This report†	Gastrocnemius	9	230
	Soleus	15	250

*Averaged values.
†Standing posture.

blood past a proximal tourniquet inflated to 90-100 mm. Hg, the implication being that the pressure developed within the deep fascia of the calf was at least of this order. Direct measurements have been made using intramuscular needles, and rather slow response measuring systems.[9,10,21] One of the difficulties with these techniques is the peculiar sickening pain[21] felt on muscle contraction which our subjects also noted if a needle was used but which was absent with the catheter technique.

Table III presents the findings of these earlier workers and ourselves. When the muscle was relaxed the pressures recorded using a catheter are quite similar to those recorded by needle. However, the pressures that we found during muscle contraction are very much greater than any except those reported by Wells and his coworkers.[21] The explanation is doubtless the absence of pain in the subjects of the present study and the rapid-response recording system.

There is some collateral evidence to support the high values that we have obtained. At only 20 to 30 per cent of maximal contraction of calf muscle, blood flow in the calf is virtually abolished[1]; in other words the pressure within the muscles approaches arterial pressure. The single muscle contractions which our subjects performed must have closely approached 100 per cent of the maximum.

2. Postural changes in calf and thigh volume. The rate of increase in volume in the calf on standing up is precisely that to be expected from the rate of arterial inflow and suggests that the venous valvu

lar mechanism is entirely competent. Dohn[7] and more recently Allan[6] using similar techniques have reported similar qualitative results.

Our findings in the thigh were unexpected. There seems to be no other explanation but that the valves in the iliac and femoral veins are not fully competent at least initially, in the face of this sort of maneuver. Yet there is some supporting evidence for our observation. We found the increase in thigh volume to be virtually complete in 10 seconds (Fig. 3); after passive foot-down tilting the pressure in the lower femoral vein is said to reach the hydrostatic level within a similar period.[7] It has been suggested that the rapid filling might be due to a very high rate of blood flow in the musculature of the thigh.[8,16] This seems to be inherently improbable and is not supported by our measurements of blood flow. Nor could upward flow from the calf be the cause, because of the lack of effect of a tourniquet at the knee. There is also some evidence from phlebographic studies that reflux of contrast medium down the femoral vein can occur in normal subjects when it is injected at the groin in the upright posture,[17,18] or when it is injected at the ankle and the subject is tilted afterward.[8,16]

Our group had previously shown that an external iliac venous valve could be demonstrated to be competent in response to a Valsalva maneuver performed in many normal subjects in a semierect posture, and other workers have shown only a slow rise in pressure in the popliteal vein with abdominal straining.[19] The explanation of these apparently conflicting results may be that with very sudden changes in pressure the valve leaflets are more effectively snapped together and held shut.

3. Changes in calf and thigh volume with exercise. A single contraction of the calf ejected about 60 per cent of the blood which had entered on standing, whereas the thigh ejected only about 20 per cent. To arrive at a true value of "stroke volume," the contribution of subcutaneous veins to the venous blood volume should be allowed for, which would give somewhat higher values.

In the calf, there is good evidence that the greater part of the venous blood is in *intra*muscular veins,[14] and clearly this will be totally ejected if intramuscular pressure rises to the levels that we have observed. Because less than 100 per cent of the venous blood is ejected from the calf by a maximal contraction, the further implication is that *inter*muscular pressure does not rise so high. Indeed, phlebography shows complete emptying of intramuscular veins with contraction of the calf but only incomplete emptying of the intermuscular veins.[3]

Although intramuscular pressures were lower in thigh muscles, they are still of an order (Table I) to overcome the hydrostatic pressure in the veins at this level. Yet only about 20 per cent of the venous blood in the thigh was ejected by a single muscle contraction. The likely explanation is that most of the venous blood in the thigh is in *inter*muscular veins, and that intermuscular pressure is comparatively low. The intramuscular venous sinuses so prominent in the calf are absent in the musculature of the thigh, and the large femoral veins are acting as "through" channels for venous blood from the lower leg.

During rhythmic exercise the venous blood in the calf is reduced by about 65 per cent, and that in the thigh by 15 per cent. The reduction of volume in the thigh is less than that due to a single contraction, no doubt because of the upsurge of blood from below, and probably also because of reflux from above.

However, although the calf pump is undoubtedly the more effective, the absolute volume of blood ejected during exercise from the thigh as a whole is at least as great as that from the calf. If the results for the segments of thigh and calf were extrapolated to the lower limb as a whole, it seems to be likely that blood volume in the thigh would be reduced by about 35 ml., and volume in the calf by 60 ml.—95 ml. in all.

At least during short term exercise, the loss of blood volume from the lower limb by venous pumping more than compensates for the potential increase due to dilatation of resistance vessels. Moreover, during the first few steps of exercise a substantial contribution to central blood

volume is made from the lower limbs.

A further deduction is that in ordinary life the venous pumps are much more effective in conserving central blood volume than are changes in venous tone. It has been estimated that from the extreme limits of venous dilatation to the extreme of venous constriction only about 25 ml of blood can be emptied from the lower limb below the knee—or by extrapolation perhaps 50 ml from the lower limb as a whole.[17] But it would appear that the muscle pumps can reduce blood volume in the lower limbs by nearly double this amount when the subject is in the standing posture.

Summary

Methods are described for measuring intramuscular pressure and changes in volume with posture and exercise in the human calf and thigh. Much greater increases in pressure than previously recorded are found in the contracting muscles. The measurements of change in volume suggest that venous valves in the thigh are not fully competent with change in posture, and that the volume of blood expelled from calf and thigh during exercise makes a significant contribution to central blood volume.

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The genesis of the electrocardiogram of patients with ostium primum defects (ventral atrial septal defects)

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In 1956 Toscano-Barboza, Brandenburg, and Burchell[1] specifically related certain electrocardiographic aberrations in patients with congenital heart disease to defects of the lower atrial septum and deformities of the atrioventricular canal. They concluded that the evidence favored a congenital aberration of ventricular excitation and that the electrocardiographic phenomena were not primarily caused by left ventricular hypertrophy consequent to mitral insufficiency. Four years later the latter two authors together with DuShane[2] reported on about 86 patients with partial and complete defects of this type. They emphasized again that in patients with low atrial septal defects, so-called ostium primum defects, associated with a cleft atrioventricular valve or with complete forms of the common atrioventricular canal, the cardinal and nearly diagnostic electrocardiographic feature is the presence of left axis deviation of the initial or early electromotive forces, and of a loop in the frontal vectorcardiogram that is early oriented in the left axis quadrant, i.e., commonly at an angle of $-30°$ to $-60°$. The influence of diverse hemodynamic states which may be present in this condition was discussed and it was stressed that these do not obscure the early vectors of diagnostic importance. It was acknowledged that some patients with a partial form of this condition or with atypical lesions questionably related to deformities of the atrioventricular canal did not show this pattern.

These results have been confirmed nearly unanimously.[3-7] The genesis of this electrocardiogram has not been clarified up until now. In some of their cases, Burchell and associates explored epicardial excitation at some preselected points. Their results revealed that the posterior and lateral epicardial surfaces were activated at a normal time. It was noted, too, that early or immediate excitation of the epicardium in the anterior interventricular groove was not so uniformly present as had been reported in the literature and as was seen by them in control cases. Therefore they considered the possibility that the early left ventricular electromotive forces in defects of this type could be related to the

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advancing excitation front in the posterolateral wall of the left ventricle, occurring at normal time with the early balancing excitation front in the anterior wall lacking because of delay and irregularity of its plane.

They offered as a "contemporary" theory that the different orientation of the advancing fronts was dependent upon an anomalous left bundle branch system.

It is evident that their approach offers the only way for a solution of this problem. Therefore, we explored during cardiac surgery the epicardial excitation in 4 patients with proved atrial septal primum defects, and large left-to-right shunts, all showing the typical vectorcardiographic abnormalities. In one of these patients an intramural electrode was introduced into the posterobasal region of the left ventricular wall.

Previous studies on the human heart have already established the normal pattern of ventricular activation[8,9] double envelopment of both ventricles starting in the area trabecularis of the right ventricle and progressing toward the posterobasal areas, activated at 70 msec. or later after the beginning of left ventricular cavity potential.

Methods

For the exploration of epicardial and intramural excitation the same methods were used that have been devised for similar studies in the normal dog heart.[8,9] The intramural electrode carried 10 terminals of 0.5-mm. diameter with 2 mm. interelectrode distance. Its surface was smooth and its tip was sharpened in order to minimize the degree of damage inflicted on the myocardium. After its introduction perpendicularly to the epicardial surface it stayed in place until it was removed. Generally the tip carrying terminal No. 1 was situated in the ventricular cavity and terminal No. 10 was just beneath the epicardial surface. Flexible wire connections to the recorder allowed the intramural electrode to move freely with the heart beat. Recordings were made of unipolar complexes of all terminals against a Wilson common terminal (Patients A, B and C) or against an electrode placed on the left leg (Patient D) and of bipolar complexes taken between consecutive pairs of terminals. The epicardial exploring electrode had a small tip diameter of 1 mm. If necessary for proper application of the electrode, the heart was rotated slightly in the opened pericardial sac. A high fidelity two-channel or four-channel cathode ray oscilloscope was used for recording on 35-mm. celluloid film. The complexes were enlarged three times, which allowed an accuracy of 1 msec. for the measurement of time relations. From these recordings, time relations were determined between the onset of left ventricular cavity potential which served as a reference and the intrinsic deflection in all complexes recorded from the epicardial surface or from the intramural terminals.

In each case during operation, a map of the epicardial surface and the recording sites was drawn. These maps were used in constructing the schematic drawing of the anterior and posterior sides of the heart employed for illustrative purposes in Figs. 3 and 4,A and B. In these figures the actual unretouched epicardial complexes are shown at the sites at which they were recorded plus the times of onset of their intrinsic deflections in milliseconds after the beginning of left cavity potential.

In a later phase of this study—when we supposed that the basic disturbance in excitation is early activation of the posterobasal wall of the left ventricle—we tried to duplicate this excitation pattern in the dog heart. In three hearts driven by electrical stimuli applied to the right atrial surface, extra pulses of 1-msec. duration were delivered to two adjacent intramural terminals situated in the subendocardial layers of the posterobasal area of the left ventricle. The delay of these extra pulses was measured in respect to time of occurrence of the driving pulses. Stimulation was begun at the end of QRS and the delay was gradually shortened. Fusion beats with an increasing degree of prematurity of excitation of the posterobasal area were made in this way. During these experiments frontal vectorcardiograms were recorded in the closed-chest preparation.

Patients

Patient A. Eight-year-old girl. The pulmonary circulation ratio [illegible]

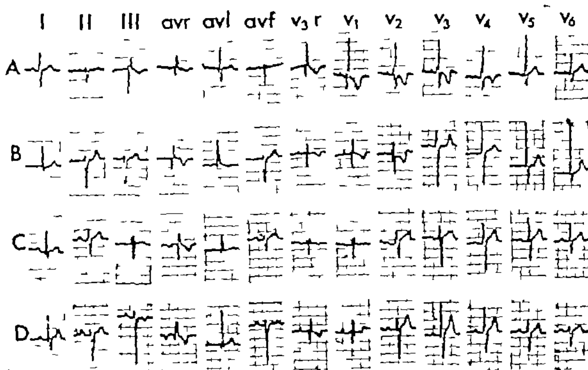


Fig. 1. Standard electrocardiograms of Patients A, B, C, and D.

right ventricular pressure was 36/5 mm Hg.

Patient B. Twenty-one-year-old man. The pulmonary circulation ratio was 3:1. The right ventricular pressure was 50/0 mm Hg.

Patient C. Fourteen-year-old girl. The pulmonary circulation ratio was 2½:1. The right ventricular pressure was 40/0 mm Hg.

Patient D. Twenty-five-year-old man. The pulmonary circulation ratio was 2:1. The right ventricular pressure was 25/0 mm Hg.

The clinical electrocardiograms and vectorcardiograms are shown in Figs. 1 and 2.

Results

Epicardial excitation

PATIENT A. Earliest epicardial activation of the right ventricle occurs at 43 msec., which indicates a delay of about 20 msec. (Fig. 3, *left section*). The unipolar complexes from the posterobasal region of the left ventricle show an rS form with early occurrence of the intrinsic deflection (28 to 33 msec.).

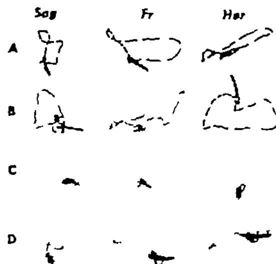


Fig. 2. Clinical vectorcardiograms of Patients A, B, C, and D. Vectorcardiograms of Patients A and B were recorded following the Frank system, with interruptions spaced at time intervals of 5 msec.; the sagittal plane recording represents the left sagittal projection. Vectorcardiograms of Patients C and D were recorded with a Sanborn vectorcardiograph following the Grishman cube system, with interruptions spaced at time intervals of 2.5 msec.; the sagittal plane recording represents the right sagittal projection.

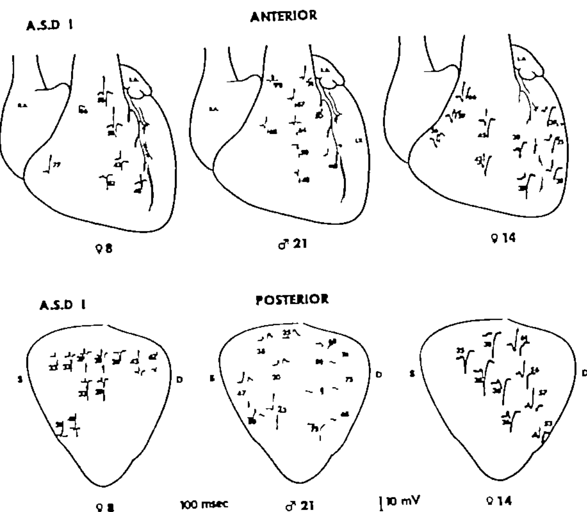


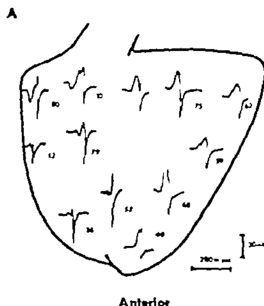
Fig. 3 Unipolar epicardial complexes from anterior and posterior ventricular surfaces recorded during operation in 3 patients with proved atrium primum defects. The numbers indicate the time of occurrence (in milliseconds) of the intrinsic deflections in the epicardial complexes after the onset of the cavity potential. The posterobasal region of the left ventricular wall is activated early

PATIENT B At the right ventricular surface (Fig 3 *middle section*) all unipolar complexes have an initial positivity and are of the rsR form with varying height of the R deflection. At the posterior side of the left ventricle the complexes near the left atrioventricular sulcus have an rS form. Here epicardial excitation occurs 30 msec. after the beginning of the reference The complexes recorded in the apical half have a q wave.

In the right ventricular complexes from the posterior side the initially positive r wave is small or may be isoelectric in the latter case giving the impression that a q wave is present There is a large time difference between the epicardial excitation times in regions to the left and to the right of the posterior attachment of the interventricular septum

PATIENT C The complexes from the anterior surface of the right ventricle have an rSR form (Fig 3 *right section*) Excitation in the area trabecularis occurs at 30 msec and is, therefore slightly delayed (10 msec)

The complexes at the anterior side of the left ventricle have a normal form no delay in epicardial excitation is present. At the posterior side it was only possible



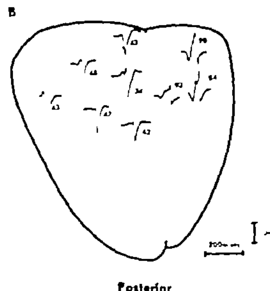


Fig. 4 Unipolar epicardial complexes from the anterior (A) and posterior (B) surfaces of the ventricles. Early excitation of the same regions as in Fig. 3 is present. Epicardial excitation of the anterior surface of the left ventricle is delayed. The dot at the posterior surface indicates the point of introduction of the intramural electrode

to record from regions close to the posterior attachment of the interventricular septum. Earliest epicardial excitation occurred at the left ventricular basal area 35 to 38 msec. after the reference.

PATIENT D Exploration of many parts of the anterior surface of the left ventricular wall could be performed revealing (Fig 4,*A*) delayed excitation of the anterior surface of the left ventricular wall (60 msec.) and early excitation (34 msec.) of the posterior basal surface (Fig 4,*B*). The QRS complex at the right ventricular surface has an rsR form epicardial excitation is delayed

In this patient in which this early activated region was readily found it was possible to determine the time relations during the recording and to localize during operation the point of earliest epicardial breakthrough. Here the intramural electrode was introduced. Excitation of subendocardial and mid mural layers occurs within the first 10-msec interval (Fig 5)

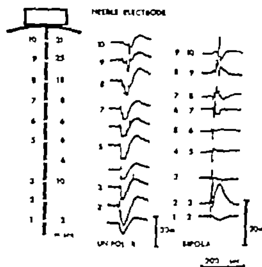


Fig. 5 Intramural unipolar and bipolar complexes from Patient D. The epicardial complexes are shown in Fig. 4. The numbers at the left side of the terminals of the intramural electrode indicate these terminals, those at the right side indicate the time of occurrence of the intrinsic deflection, in milliseconds, after the onset of the left ventricular cavity potential. Early excitation of the intramural layers is present.

Discussion

In all instances, excitation of the right ventricular subepicardial muscle was delayed in a varying degree. The number of points explored was too small for us to draw conclusions about the pattern of excitation of the right ventricular surface. It is interesting that epicardial points overlying and at both sides of the anterior attachment of the interventricular septum are activated with small differences in time, whereas at the posterior attachment of the ventricular septum there are large differences in time of arrival between the posterobasal part of the left ventricle and the adjoining part of the right ventricle (30 to 40 msec.) This finding may be partly related to the absence or scarcity of subendocardial Purkinje fibers in this part of the right ventricle and to a relatively slow conduction velocity of 30 cm. per second in the human heart, compared with 50 cm. per second in the canine heart.[9]

In patients with other types of congenital heart disease it was possible to record Purkinje activity from the right ventricle by way of intramural terminals situated in the subendocardial layers, and to estimate the presence of a delay in ramifications of the right bundle. In patients with septum primum defects, no intramural electrodes could be applied to the right ventricular wall because the exploration of epicardial excitation already consumed the limited time available. The form of the epicardial and intracavity complexes of the right ventricle is consistent with a same degree of conduction delay in the right bundle branch.

The greatest differences in left ventricular excitation as compared with normal are present at the basal region of the posterior wall near the posterior attachment of the ventricular septum. In our patients of varying ages with normal hearts, in whom the exploration of that area was possible, the earliest epicardial activation time found was 70 msec. after the beginning of the left ventricular cavity potential,[9] whereas in the patients with ostium primum defects, values of 28 to 34 msec. are found. Therefore, we consider this finding to be highly suggestive of the existence of a relatively large posterobasal area activated at least 30 msec. earlier than normal. In the only case in which intramural excitation of that area could be studied, the findings were consistent with very early activation of the subendocardial layers of this part of the ventricular wall (Fig. 5). In Patient C (14-year-old girl), in whom some parts of the anterior left ventricular surface were explored, no delay was found, but in Patient D, epicardial excitation of that region was markedly delayed.

Do these findings explain the typical electrocardiographic and vectorcardiographic features in defects of this type? This question has to be answered with due consideration of the fact that multiple insertions of intramural electrodes were not possible and that, therefore, no complete data about the time of occurrence of subendocardial activation of the left and right ventricular walls are available. We may assume, however, that changes in epicardial excitation time reflect corresponding changes in subendocardial excitation time.

Early excitatory forces are present in the posterobasal region of the left ventricular wall. During their outward spread toward the epicardium they probably progress mainly in a posterior and inferior direction. In the posterolateral part of the left ventricle, excitatory fronts will have a more superiorly directed orientation. The influence of excitatory forces in the adjoining part of the ventricular septum, which could also be superiorly oriented, cannot be ascertained at the moment. Considering only the electrical effect of the early activated posterobasal region, one would expect a displacement of the successive initial vectors in a posterior and inferior direction up to the moment of epicardial breakthrough. In the vector loops of our 4 cases, however, this change could not be demonstrated. The time course of the very first part of the frontal vector loop appears to be within the normal limits. It is probable that the excitatory waves in the lateral wall of the left ventricle cancel or diminish this effect. After epicardial breakthrough at the basal part of the posterior wall, however, the excitatory forces at the anterior and posterolateral parts of the left ventricle, progressing in a more superior direction, suddenly predominate, resulting in an abrupt change in this direction of the vector

forces probably increased if a delay in the anterior part of the left ventricle is present. It is possible that this part of the vector loop indicates the time of occurrence of epicardial breakthrough of the posterobasal region

In our patient D the sweep in a superior direction occurred about 35 to 40 msec after the beginning of the QRS in Lead I whereas earliest epicardial breakthrough occurred at 35 msec The form of the epicardial complexes of the right ventricle is consistent with a smaller or larger degree of conduction delay in the right bundle branch but more data are necessary before we can decide whether other factors play a role The swing to the right in the frontal vector loop is caused by right ventricular excitatory forces becoming predominant after epicardial breakthrough at the anterior side of the left ventricle. The excitation pattern in the right ventricle determines the final part of the loop

At this point returning to the epicardial excitation studies of Burchell and associates[3] we may point out that also in one of their cases (depicted in their Fig 6) apical and posterolateral surfaces of the left ventricle were excited 0 01 to 0 02 second earlier than the anterior basal surfaces (0 03 versus 0 04 to 0 05 second) In the other patient with typical ASD-I activation at different points on the posterior surface was normal (0 065 to 0 080 second) but a delay in activation of the anterior part of the left ventricular wall was found at the basal part of the anterior interventricular groove, epicardial excitation time was 0 065 second at the apex it was 0 035 0 037 and 0 035 second

In 2 other cases no excitation of the left ventricular epicardium near the anterior interventricular groove was found within 0 000 to 0 005 second after the onset of QRS in a peripheral reference lead also indicating a delay Therefore they suggested that early left ventricular forces could be related to the advancing excitation front in the posterolateral wall of the ventricle with the usual early balancing excitation front in the anterior wall being lacking " but stressed that the preliminary data were inadequate to prove this concept It has to be pointed out that the results of our excitation studies cannot be compared with these figures, because we used the beginning of the right or the left ventricular cavity potential as reference for our measurements, whereas Burchell and associates used a peripheral limb lead which may cause differences in measurements of about 20 msec In one of the 2 patients in whom the anterior left ventricular surface was explored a delay in excitation was present

Anatomy of specific conduction system During this study when we assumed from the electrophysiologic data that short communications between the main bundle or A V node and the posterobasal area could be present we learned that Verduyn Lunel[19] studied the anatomic structure of the specific conduction system in this condition. He did not find an undivided initial part of the left bundle branch because it bifurcates very soon after its origin into two rather well-defined fasciculi a ventral (anterior) one and a dorsal (posterior) one The latter declines abruptly in the direction of the apex giving off small branches to the posterobasal region of the septal wall This conspicuous feature was not seen in the normal heart The ventral fasciculus is seen to be more or less parallel to the basal free border of the interventricular septum

Stimulation experiments Because of the similarity in excitation patterns of dog and human heart we tried to reproduce this excitation pattern in the dog by transferring excitation of the subendocardial layer of the posterobasal region of the left ventricle, normally activated 10 to 15 msec after the beginning of ventricular depolarization to an earlier moment in the QRS interval Stimulation of the subendocardial layer of the posterobasal region of the left ventricle was begun at the end of the QRS complex and the time interval between driving and extra pulses was gradually shortened In Fig 6 it can be seen that the complexes in standard leads changed from normal to fusion complexes with an increasing extrasystolic component When the extra pulse fell before the expected time of occurrence of the QRS (delay 165 msec) a ventricular premature beat occurred. The vector loops of the fusion beats show an increasing upward shift of early parts of the loop and

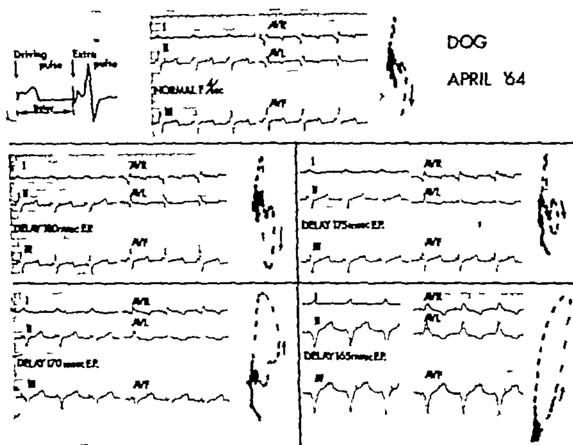


Fig. 4. Standard leads recorded with Elema Mingograf 42 B, paper speed 100 mm. per second, and frontal vector loops recorded with a Sanborn vectorcardiograph following the Grishman cube system during experiments on the dog heart. Interruptions of the vectorcardiogram are spaced at time intervals of 2.5 msec. An intramural electrode was introduced into the posterobasal region of the left ventricular wall. Driving stimuli were delivered to the right atrium. Extra pulses were delivered to two adjacent terminals of the intramural electrode which were situated in the subendocardial layer. The delay indicates the time interval between driving stimuli and the extra pulse. Transfer of excitation of the posterobasal area to an earlier part of ventricular depolarization results in an increasing upward shift of early parts of the vector loop with anticlockwise rotation.

the occurrence of anticlockwise rotation of that part.

Summary

The typical vectorcardiogram in partial and complete forms of defects of the atrioventricular canal has a characteristic pattern with anticlockwise rotation of the "initial" major part of the QRS loop and position above the isoelectric line. In 4 hearts with surgically proved atrial septal defects of the primum type, early excitation of the posterobasal region of the left ventricle was found occurring 28 to 35 msec. after the beginning of ventricular depolarization, whereas values of 70 msec. or more were found in normal hearts. Because the first part of the loop does not deviate clearly from the normal, the early excitatory forces in that part of the left ventricular wall, progressing in posterior and inferior direction, are probably mainly balanced by those already present in the lateral part of the left ventricular wall. The contribution of septal excitatory forces which could progress in a superior direction could not be ascertained. The abrupt shift to the left and in upward direction occurring approximately in the 30 to 40-msec. interval, is caused after the disappearance of outward-spreading excitatory forces in the posterobasal part of the left ventricular wall by now unopposed excitatory forces in the lateral and anterior parts of this ventricle.

A delay of excitation in the anterior part of the left ventricular wall if present will augment this shift of vectors. The right ventricular conduction delay accounts for the form and location of the terminal part of the vector loop

Because of the great resemblance in excitation between the dog and human heart we tried to reproduce this excitation pattern in the dog heart by progressively transferring excitation of the posterobasal part of the left ventricular wall to an earlier moment of the QRS complex Frontal vector loops from these fusion beats, transitional in form between normal beats and premature beats originating in this region were registered showing a gradual displacement of early parts of the loop in a superior direction and the occurrence of anticlockwise rotation

Our sincere thanks are due to Prof Dr A. G Brom and Dr N G Meyne for their cooperation which made this study possible

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Localization of lobeline-sensitive receptors in the pulmonary circulation in man

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Rapid intravenous injection of lobeline is used to measure the circulation time from an arm vein to the systemic circulation by the interval elapsing from the intravenous injection to the appearance of cough and hyperventilation.[1] These effects are believed to result from the stimulation of the carotid body chemoreceptors.[2] In a study in normal subjects, Eckenhoff and Comroe[3] observed cough within 8 seconds after the intravenous administration of lobeline, preceding the hyperventilation, and they assumed that the cough-inducing receptors are located in the pleura or respiratory tract. In the present investigation we attempted to locate the lobeline sensitive receptors that induce cough in the pulmonary circulation. This was achieved by injecting the drug into different sites of the pulmonary artery, into the left ventricle, and into the descending aorta, and measuring the time of appearance of cough.

Materials and methods

Six patients with mitral stenosis and 2 healthy subjects were studied. The 2 normal subjects were women, one 24 and the other 26 years of age, whereas the group of patients with mitral stenosis consisted of 4 women and 2 men who were between 18 and 34 years of age. All patients were in sinus rhythm and no signs of peripheral venous congestion were present. In all subjects a right heart catheterization was performed in the usual manner. A No. 7 Cournand catheter was placed in the distal part of the right or left pulmonary artery. The catheter was not in a wedge position as confirmed by roentgenogram and pulmonary arterial pressure recording and by the ability to withdraw blood through it. After the subject had rested 10 to 15 minutes, 3 mg. of lobeline† diluted in 1 ml. of normal saline was injected through the catheter, which had been prefilled with the solution in order to avoid errors due to dead space. The precise lapse of time from the beginning of the injection until the appearance of cough was recorded. After a time interval of 10 minutes the catheter was placed into the main branch of the right or left pulmonary artery just distal to the bifurcation, and lobeline was again injected. In 2 patients with mitral stenosis retro-

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†Lobeline hydrochloride, Sandoz A. G., Basle, Switzerland.

grade left heart catheterization was performed through the right brachial artery and the catheter was placed into the left ventricle and subsequently into the descending aorta just distal to the origin of the left subclavian artery. Lobeline in the same dose as mentioned above was then rapidly injected into these sites, with a 10-minute time interval between each injection.

Results

Seventeen injections of lobeline were administered, 7 being given into the extrapulmonary part of the right or left main pulmonary artery, 6 into the intrapulmonary part of these arteries, 2 into the left ventricle, and 2 into the descending aorta. Cough was a constant feature after injection of the drug into the main branch of the right or left pulmonary artery in the patients with mitral stenosis as well as in the normal subjects (Fig. 1). No difference in the intensity of cough was observed between the two groups. On the other hand no cough was observed when lobeline was injected into the intrapulmonary part of the right or left pulmonary artery, or into the left ventricle or the descending aorta in the normal subjects and in the patients with mitral stenosis (Fig. 2).

Discussion

Although receptors sensitive to lobeline are generally assumed to be located in the systemic circulation, it was suggested by Eckenhoff and Comroe that the receptors which induce cough might be present

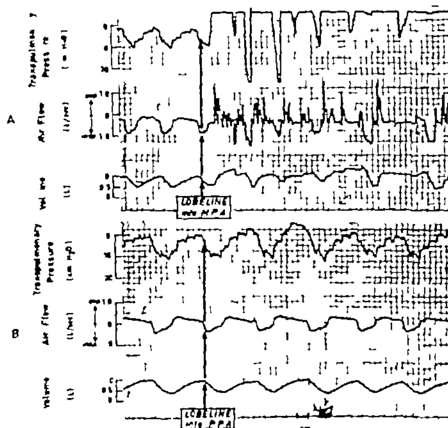


Fig. 1. Injection of 3 mg. of lobeline into the right main pulmonary artery (M.P. 1.) and the peripheral part (P.P. 1.) of the pulmonary artery in a healthy subject. Note the appearance of cough within 1.2 seconds after lobeline was injected into the M.P.A. (extrapulmonary part) and the marked transient rise in transpulmonary pressure whereas no change occurred when the drug was injected into the P.P.A. (intrapulmonary part). Vertical arrow indicates the time of injection. Paper speed 10 mm. per second.

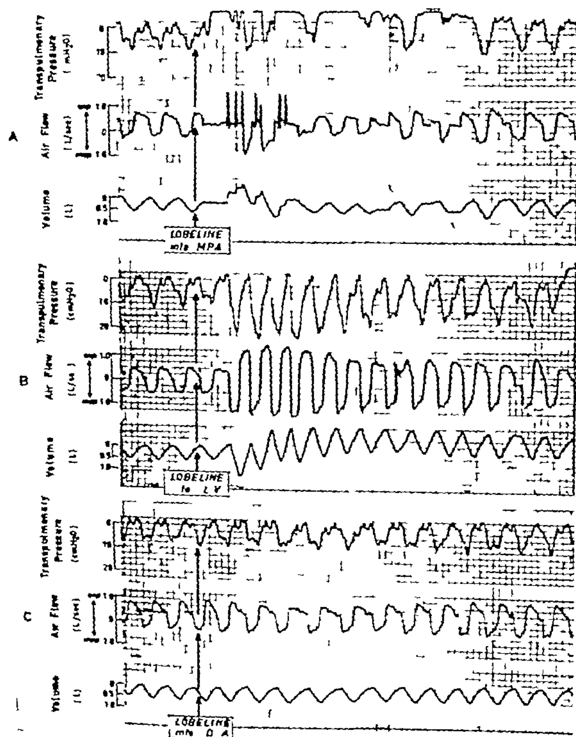


Fig. 2. Injection of 3 mg. of lobeline into the left main pulmonary artery (*M.P.A.*), the left ventricle (*L.V.*), and the descending aorta (*D.A.*) in a patient with mitral stenosis. Note the marked increase in transpulmonary pressure within 1.0 second, and the irregularity in air flow and volume indicating cough after lobeline was injected into the M.P.A. Injection of the drug into the L.V. caused hyperpnea in 2.2 seconds, whereas no change occurred after injection into the D.A.

in an area supplied by the pulmonary circulation.[3] Similar results were obtained by us in healthy subjects,[4] in whom cough constantly preceded hyperventilation and appeared within 4 to 6 seconds after the intravenous injection. In order to prove that a sensory receptor with a certain localization responds to chemical agents, the following criteria have to be fulfilled according to Comroe[5]: (1) administration of such a substance very close to the receptor cells should cause within 1 to 2 seconds a typical pattern of stimulation, and (2) section or blocking of the afferent nerve fibers should abolish it. In the present study, lobeline was injected therefore into the different segments of the pulmonary artery and the systemic circulation, and the precise lapse of time from the beginning of the injection until the appearance of cough was recorded.

Injection of lobeline into the extrapulmonary part of the pulmonary artery resulted in cough within 1.0 to 1.4 seconds. This was true whether the drug was administered into the main pulmonary artery or its right or left branch, but always near the bifurcation. On the other hand, injection of lobeline into the intrapulmonary part of the pulmonary artery distal to the bifurcation, as well as into the left ventricle or into the descending aorta, did not evoke any cough. Our findings indicate, therefore, that in man the sensory endings which are stimulated by lobeline and induce cough are located near the bifurcation of the pulmonary artery. Bevan and co-workers[6,7] demonstrated in cats receptors with similar localization in the pulmonary artery, stimulation of which by lobeline caused systemic hypotension and depression of ventilation. Krahl[8] found at the same site, i.e., on the posterior surface of the pulmonary trunk just behind the bifurcation, small, highly vascular structures histologically resembling the carotid and aortic bodies. Moreover, he demonstrated that the innervation of these structures arrives from the vagi and that the supply of blood comes from a small branch of the pulmonary artery. Since these are the basic components of a glomus, Krahl named these structures "glomus pulmonale." However, as yet no physiologic or functional significance of the glomus pulmonale has been demonstrated, in so far as we know. Perfusion of the pulmonary circulation with anoxic blood[19] or with blood that has a high CO_2 content[10,11] failed to cause any response in ventilation; therefore, this glomus cannot as yet be regarded to be a true chemoreceptor. However, our evidence that there are chemosensitive receptors able to respond to a pharmacologic stimulus with an important respiratory reflex might suggest a physiologic significance of the glomus pulmonale.

In another of our studies,[4] injection of 3 mg. of lobeline intravenously produced cough in all 10 healthy subjects, but in only 3 of 10 patients with mitral stenosis. In the present investigation, the same amount of the drug was injected straight into the pulmonary artery, increasing obviously the concentration of the drug reaching the receptors in the pulmonary circulation. This higher concentration of the drug sufficed to evoke cough not only in all the normal individuals, but also in all patients with mitral stenosis. This may point to an increased threshold of sensitivity of these receptors in patients with mitral stenosis. It may be assumed that the chronically increased pressure in the pulmonary circulation and/or changes in the mechanical properties of the lung may be responsible for this.

Summary

Lobeline injected into the extrapulmonary part of the right or left branch of the main pulmonary artery, near the bifurcation, induces cough within 1.0 to 1.4 seconds, whereas no cough appears after injection of the drug into the intrapulmonary part of these arteries or into the left ventricle or the descending aorta. This shows that the cough-provoking chemoreceptors which are sensitive to lobeline are situated in man near the bifurcation of the pulmonary artery. No difference in response was observed between the 2 normal subjects and the 6 patients with mitral stenosis.

The technical assistance of Mrs. T. Schwartz and Mr. J. Fischer is gratefully acknowledged.

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The electrical interaction between artificial pacemakers and patients, with applications to electrocardiography

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Although a variety of implantable artificial pacemakers have been in common use for the past 4 years, very little is known about the physical interaction of pacemaker currents with the myocardium and other body tissues. The present studies were undertaken to gain insight into the afore-mentioned interaction and to examine in detail the relationship between a known source of current (the artificial pacemaker) in the heart and the resulting body surface potentials. The latter relationship yields significant information concerning frequency distortion produced by the transmission of electrocardiographic currents through the body.

Method

Prior to surgery, each of eleven pacemakers† was calibrated as follows. A wide-band (0 to 50 megacycles per second) oscilloscope‡ was used to display the open circuit voltage and then the voltage across each of at least ten 1 per cent resistors sequentially connected to the unit. For every such load the pacemaker voltage pulse was photographed at three sweep

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†Ten Medtronic Model 5860 and one Model 5870, all with helical platinum-iridium leads and electrodes.
‡Type 547 Tektronix with CA amplifier.

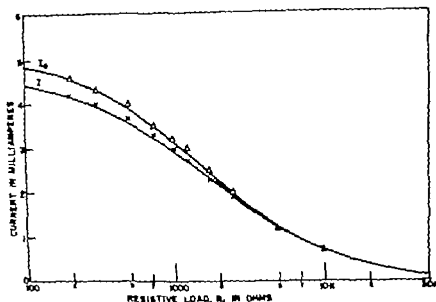


Fig. 1 Pacemaker calibration showing data obtained from unit subsequently implanted in Patient 11. Triangles and crosses indicate currents at the beginning (I_B) and end (I_T) of pulse respectively. Solid lines are theoretical curves based on an equivalent circuit for the pacemaker. See text.

speeds, each chosen to best record the total pulse (0.5 msec. per centimeter) and its rising (0.5 μsec per centimeter) and falling (5.0 μsec per centimeter) phases. The total pulse pictures show what will be referred to as the slow portion of the pulse. Voltage amplitudes were measured at the beginning and end of the pulse, and the corresponding currents, I_B and I_T, were calculated by dividing by the load resistance R_L. The data were plotted as a function of resistive load R_L. A typical graph is shown in Fig. 1.

During surgery the pacemaker current was measured at the time of implantation or replacement.[1] A current probe and pre-amplifier* with a 50-c.p.s. to 50-megacycle bandpass was used for measurements in the pacemaker circuit now completed by the myocardium. This type of probe was utilized because it is constructed of materials which have resisted sterilization with ethylene oxide (Cry-oxide).† Moreover, since the current probe is an inductive device which measures current in insulated wires, it presents a minimum hazard of shock to the patient. The metallic interior of the probe jaws is grounded in normal use.

After surgery the total pulse and its rising and falling phases were recorded between at least one precordial point and a right arm reference connection.* Standard precordial and extremity electrodes were used. Photographs of the slow portion of the voltage pulse recorded at a sweep speed of 0.5 msec. per centimeter (Fig. 5) were optically enlarged and the amplitude of the waveform was measured every 0.25 msec. beginning with the instant of rise, and plotted on semilogarithmic paper.

Results

1. Calibration. The shape of the voltage or current pulse from resistively loaded pacemakers of the type utilized is a trapezoid, an example of which appears in Fig. 2. The pulse duration ranged from 1.5 to 2.0 msec. for the units studied. Table I shows that the ratio of the magnitude of the rising portion of the pulse to the falling part (I_B:I_T) never exceeded 1.1 for the resistive loads used (200 to 25,000 ohms). These calibration data can be rationalized by equating the pacemaker with a capacitor C_o in series with a resistor R_o, and an ideal switch (Fig. 3). The switch is closed

*Hewlett-Packard Model Numbers 1110A and 1111A.
†Fifteen pounds per square inch for 24 hours.

*Type O "Modified" Tektronix preamplifier powered by 2127 supply provided bandwidth of 0 to 20 megacycles per second.

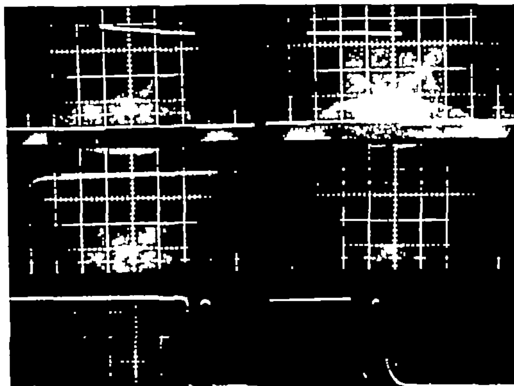


Fig. 2 Calibration record from the pacemaker implanted in Patient 11. Each square is a centimeter on a side. The column on the left was obtained with a 500-ohm load (0.5 volts/cm.) whereas a 10,000-ohm load was used for the records on the right (2.0 volts/cm.). The upper row shows the total pulse or slow portion (abscissa = 0.5 msec./cm.), the middle row shows the rising phase (abscissa = 0.5 μsec/cm.), and the lower row shows the falling phase (abscissa = 5.0 μsec/cm.)

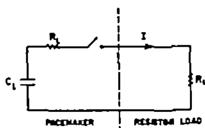


Fig. 3 Equivalent circuit of pacemaker connected to a resistive load used during calibration.

allowing the capacitor which had been charged to an initial voltage of E_o volts, to discharge into an external load through R_I. After time T the switch is opened and the capacitor is recharged to E_o. The cycle is repeated at a fixed rate typically 75 pulses per minute.

The results shown in Fig. 1 are characteristic of ten of the pacemakers included in this study. This unit had an open circuit voltage of 8.2 volts. The solid lines are theoretical curves obtained from Equations (2) and (3) of the Appendix, using C = 10 μf, R_I = 1,600 ohms, and E_o = 8.2 volts. The symbols are calibration data for this unit. The maximum discrepancy shown (4 per cent) is within experimental error. One unit had a variable current output achieved with a series rheostat. Calibration data on this unit taken with the same adjustment used at surgery showed that R_I was 1,000 ohms. In summary, calibration data for the eleven pacemakers were consistent with the equivalent circuit of Fig. 3 in which C_I was 10 μf in all cases and R_I was 1,600 ohms in ten instances and 1,000 ohms in one.

The equivalent circuit discussed in the preceding paragraph is consistent with the published circuit (a 1,500-ohm current-limiting resistor or a rheostat, a 10-μf capacitor and a transistor which

acts as a switch*) provided that a resistance of 100 ohms is assigned to the transistor and its associated circuit during the time it conducts and acts as a closed switch One unit was recalibrated with the 1,500-ohm series resistor temporarily shorted out. The open-circuit voltage was 8 0 volts. Measured values of I_o and I_T were compared with values calculated from Equations (2) and (3) of the Appendix, taking $E_o = 8.0$ volts, $C_1 = 10$ µf and $R_1 = 100$ ohms. Agreement within 3 per cent was achieved for all values of I_o less than 20 Ma. Hence, for all currents of interest, the transistor and associated circuit contribute 100 ohms which must be added to the limiting resistance present to obtain R_1 in the pacemaker equivalent circuit of Fig 3

When examined with a fast time base (0.5 µsec per centimeter) the average rise time* of the pacemaker pulse is 0.82 µsec, with a range of 0.4 to 1 15 µsec (Table III) Some units display an inflection at the midpoint of the rise when resistive loads of less than about 1 000 ohms are utilized The falling phase of the pulse consists of a rapid return to the base line (with resistive loads of less than 1 000 ohms) followed by one or more rounded "bounces" each lasting about 2 µsec.

2 Measurements of current during surgery When the pacemaker with the calibration records shown in Figs. 1 and 2 was implanted, the current pulse in Fig 4 was obtained The configuration of current pulses obtained at surgery in the ten other cases was similar The response of the current probe falls off for frequencies below 50 cycles per second and consequently the pacemaker pulse appears to droop when examined at the slower sweep speeds (0.5 msec. per centimeter) appropriate for display of the entire pulse. Accurate measurements can be made of the magnitudes of the rise (I_o) and fall (I_T) current because these portions of the stimulus are high-frequency events not subject to distortion by the low-frequency limitations of the probe. I_o ranged from 3.2 to 5.2 Ma., with an average value of 4 0 Ma. Table I shows that the ratio I_o/I_T in these records averaged 1 4 (1.2 1.5)

*The time (µsec) from the instant of rise to the major inflection point.

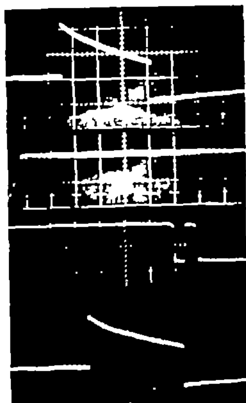


Fig 4 Records of pacemaker current obtained with a current probe. The upper three photographs are records of pacemaker current obtained from Patient 11 during implantation. Uppermost is the slow portion and beneath it are, respectively the rising and falling phases of the pacemaker pulse. The lowest record is the slow portion of the current pulse delivered to an equivalent circuit of the patient load (*see text*) constructed with components calculated for this patient. Ordinates 2 Ma cm. abscissae as in Fig 2.

significantly greater than the maximum value of 1 1 during resistive calibration

The fine structure of the rising and falling phases of the stimulus observed during surgery was virtually identical to that observed during calibration when similar peak current was present (Table II and Figs. 2 and 4)

3 Pacemaker pulses on the body surface In all but 2 patients, both myocardial electrodes were utilized to deliver impulses to the heart (bipolar stimulation) In these 9 the peak stimulus artifact on the thorax was never more than 6 mv When the output of the pacemaker was administered between a single myocardial electrode and an abdominal subcutaneous

Table I. Rise/fall ratios and currents of pacemaker pulses

Patient number	Calibration	Surgery			Surface
	I/Ir	I' (MA)†	I'r (MA)†	I'/I'r	V/Vr
1	1.1	4.0	4.0	1.1	1.3
	1.1	4.0	2.9	1.4	1.4
3	1.1	3.8	3.0	1.1	1.4
4	1.1	3.4	.9	1.2	1.4
5	1.1	4.1	3.0	1.4	1.3
6	1.1	4.5	3.3	1.4	1.3
7	1.1	3.6	2.8	1.3	1.4
8	1.0	3.2	2.1	1.5	1.4
9	1.0	5.2	3.5	1.5	1.4
10	1.0	4.1	3.2	1.3	1.3
11	1.1	4.2	3.0	1.4	1.4

*Unipolar stimulation.
†Maximal values.
I = Magnitude of current at beginning (rise) of pacemaker pulse during calibration. Ir = Magnitude of current at end (fall) of pacemaker pulse during calibration. I' = Magnitude of current at beginning of pacemaker pulse after implantation at surgery. I'r = Magnitude of current at end of pacemaker pulse after implantation at surgery. V = Magnitude of body surface voltage artifact at beginning of pacemaker pulse. Vr = Magnitude of body surface voltage artifact at end of pacemaker pulse.

Table II. Rise times (µsec) *of pacemaker pulses*

Patient number	Calibration	Surgery	Surface
1	0.6	0.4	0.7†
2	0.6	0.5	0.3
3	1.1	1.0	—
4	1.1	0.9	—
5	0.7	0.5	1.1†
6*	1.0	0.9	0.9
7	1.2	0.9	0.9
8	1.2	1.2	1.0
9	1.1	1.2	—
10*	0.8	0.8	1.1
11	0.5	0.4	0.4

Time (µsec) from the onset of the pulse to the major inflection point.
*Unipolar stimulation.
†Preamplification with Tektronix Type D unit. All others utilized Modified Type G.

site adjacent to the pacemaker case, the stimulus artifact attained values as high as 40 mv. The rise time of the pacemaker voltage pulse was measured *in all but three* instances in which low amplitude precluded triggering of the necessarily rapid sweep (0.5 µsec per centimeter). It is apparent from Table II that the rise time on the body surface for a given pacemaker is of the same order noted during measurements of current at surgery and earlier at calibration. In two instances in which rise times were somewhat slower on the body surface than elsewhere, the preamplifier utilized* had a limited high-frequency response and could not be expected to follow the swiftly rising portion of the pacemaker pulse. The modified type G amplifier used in all other measurements of voltage has a rise time capability of 0.25 µsec and amplifies the pacemaker pulses without distortion. These data show that waveforms with rise times of the order of 1 µsec are conducted from the *myocardium to the body surface without* significant distortion.

*Type D Tektronix.

The slow portion of the pulse, on the other hand, showed readily apparent differences among the pictures taken at calibration, implantation, and on the body surface. Photographs of the body surface voltage artifacts from Patient 11 are shown in Fig. 5.

Analysis of the slow portion of pacemaker pulse. The electrical characteristics of body tissues have been shown by others[4] to be substantially resistive and independent of frequency in the range of 1 to 10,000 cycles per second. These properties of body tissues, as well as the lack of distortion of portions of the pacemaker pulse with frequency content well beyond this range, suggested that the slow portion of the pulse at the body surface would follow closely the current delivered to the myocardium. As a preliminary check, the ratio of rise to fall voltage amplitudes, V/Vr, was computed for each pulse recorded.

Considerable variation was noted in the shape of the voltage pulse in the case of one of two patients with "unipolar" arrangement of stimulation electrodes. Since the shape of the current pulse at surgery was not unusual, it is likely that the variation in voltage waveform noted was due to polarization at the surface electrodes. For this reason, no further analysis of either case with "unipolar" electrodes is included.

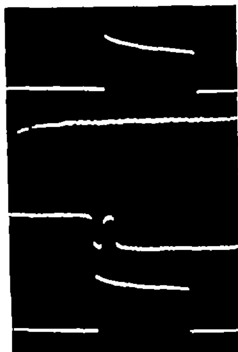


Fig. 5 The upper three photographs are voltage artifacts from the precordium of Patient 11 after recovery from surgery. The record at the top is the slow portion, and beneath it are, respectively, the rising phase and the falling phase of the pacemaker pulse. Sensitivity 2.5 mv./cm. The lowest photograph is the slow portion of the current pulse delivered to the patient's equivalent circuit by a similar pacemaker. Oscilloscopic gain was adjusted to produce deflections comparable to those in the top photograph. Abscissa as in Fig. 2.

from the surface. These data are summarized in Table I. In each case the surface voltage ratio obtained agreed with the implantation current ratio within experimental error. Consequently, it was tentatively assumed that the shape of the slow portion of the voltage pulse at the surface was not significantly different from the current pulse delivered to the myocardium.

The semilogarithmic plot of the slow portion of the pulse was a straight line except for the first three or four values. Differences between this line and the first three or four values were replotted and defined a second straight line on semilogarithmic paper. The slow portion of the pacemaker pulse may thus be described in terms of two exponential functions or time constants. The latter observation indicates that two capacitors are needed in a circuit analogue of the tissue load on bipolar pacemaker electrodes. The equivalent circuit shown in Fig. 6 has been utilized. Values for each component were determined for each case (Table III) utilizing formulae derived in the Appendix, and the following variables: (1) the rise (peak) current (I_0) measured at surgery, (2) the ratio (B/A) of the zero time intercepts of the fitted straight lines on the semilogarithmic plots, and (3) the time constants (τ and τ') of the foregoing plots. τ (or τ') is the time when the voltage had fallen to e^{-1} or 36.8 per cent of its peak value.

An equivalent circuit was constructed utilizing values calculated from measurements on Patient 11. The current pulse delivered to this circuit by a pacemaker of the same type actually implanted in this patient was measured by placing an oscilloscope across R. The pulse observed was

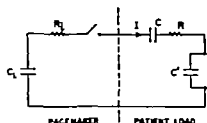


Fig. 6 Equivalent circuit of pacemaker connected to the equivalent circuit used to represent the patient load.

Table III. Values for equivalent circuit of patient load impedance

Patient number	R (ohms)	C (μf)	R′ (ohms)	C′ (μf)
1	550	6.0	290	1.4
2	500	9.7	325	1.1
3	600	4.1	95	2.0
4	870	5.5	115	4.5
5	450	5.6	180	1.6
7	700	5.4	270	1.2
8	1,000	2.8	185	1.6
9	320	10.2	115	1.1
11	350	5.5	335	0.8

*Replacement of pacemaker unit without thoracotomy.

virtually identical to the voltage pulse present on the patient's thorax (Fig 5). The current waveform in this system was determined with the current probe (Fig 4) and it too was almost identical to the current waveform recorded at implantation. In this way confirmation was obtained for the tentative assumption that the slow portions of the voltage pulses observed at the body surface have the same configuration as the current pulses delivered to the myocardium.

Discussion

Although artificial pacemakers of one make were employed in this work, it will become evident that the current-voltage relationships derived have general significance.

Two frequency-dependent electrical impedances are implicit in the foregoing studies. The first, a transfer impedance independent of both pacemaker and electrode types, relates the voltage artifact at the body surface to the pacemaker current delivered to the myocardium. The second, which may be designated the patient load,[3] is the total in vivo impedance placed upon the pacemaker electrodes. Patient load is a function of two classes of variables. The first class is independent of the particular electrodes utilized but includes such variables as current density, frequency spectrum of pulse, electrode separation, tissue impedance, etc. The other class is dependent upon the type of electrodes and involves variables such as the electrode material and configuration. It follows that pacemakers of any type utilizing Chardack platinum-iridium electrodes will have a load of similar characteristics placed upon them, provided that variables of the first class are accounted for as in these studies.

The most direct way of obtaining the patient load impedance would be to record simultaneously voltage and current at the myocardial electrodes after they are connected to the heart at surgery. However, the voltage measurements require direct myocardial connection of electronic equipment energized from power lines, with the attendant hazard of ventricular fibrillation. Current, on the other hand, was measured safely with a current probe. The necessity for voltage measurement at the electrodes during surgery was circumvented by determining the equivalent circuit for the pacemaker (Fig 3) as part of the calibration procedure. The pacemaker equivalent circuit, together with knowledge of the current at surgery, enabled calculation of the patient load impedance and its expression as another equivalent circuit, which is shown in Fig 6. Values for the four elements of the latter equivalent circuit are listed in Table III.

A consideration of the deformation of pacemaker pulses by the myocardium has led others to prepare substantially different equivalent circuits of the pacemaker load. One such circuit[3] was prepared for a device employing stainless steel loop electrodes. In another case the "synthetic load" failed to account for the in vivo load with the fidelity achieved in the present study.

The slow portion of the pacemaker pulse is characterized by two time constants. The shorter is typically 0.2 msec., and the larger sometimes exceeds 10 msec. Therefore, important frequency components are present in the range from a few cycles per second to several kilocycles per second. Schwan and Kay[4] showed that this frequency range is one in which tissues such as muscle are well characterized by constant resistivity and concluded that electrocardiograms containing components up to a thousand cycles would not be distorted. It is reasonable then to expect that the myocardium and surrounding tissues contribute resistance alone to the patient load impedance in the frequency range encompassed by the slow portion of the pulse. This resistance, which depends on electrode separation, is represented by a fraction of the resistor R in the equivalent circuit of Fig 6. The remainder of the equivalent circuit is attributable to polarization at the electrode-myocardial interface. Polarization is an electrochemical interface phenomenon and involves, among other things, the movement of ions after the application of an electrical field.[5] It is concluded that electrode-myocardial polarization rather than tissue impedance accounts for the deformation of the slow portion of the pacemaker pulse.

Measurements of current at surgery were obtained either when the chest wall

was partially open after electrode implantation or after a replacement pacemaker had been inserted without a thoracotomy. The four highest values for R occur in instances in which the electrodes were newly implanted, yet the next to lowest value for R is present in a fifth such case. Since a substantial portion of the total equivalent circuit for the patient load is attributable to polarization at the myocardial-electrode interfaces, the effect of thoracotomy, if any, should be a relatively small change in the series resistor R.

The equivalent circuit for the patient load has a series capacitor C (Fig. 6); an infinite impedance to direct current is therefore implied. However, this circuit was derived from a study of the distortion of the slow portion of the pacemaker pulse which has no significant components below a few cycles per second. Put in slightly different terms, the capacitor C can be shunted by high resistance (greater than 1,000 ohms) without noticeably changing I, the current which the pacemaker would deliver to this equivalent circuit.

Transfer impedance is of direct interest to electrocardiography because it relates a known myocardial current to body surface potentials in an in vivo human experiment. The rise of the pacemaker pulse contains frequency components in the frequency range of 10^4 to 10^4 c.p.s. In this part of the frequency spectrum the electrical properties of representative tissues enter a frequency-dependent region designated the β dispersion.[4] However, electrocardiographic analysis is not so much concerned with the details of the frequency dependence of the transfer impedance as with possible distortion of waveforms. Readily measured impedance variations with frequency obtained with the alternating current technique[11] may have only a small effect on a particular waveform. With the precision of measurement available, pacemaker voltage pulses at the body surface were observed to have the same shape as current pulses delivered to the myocardium, which suggests that distortion is small for frequency components up to 10^4 cycles per second. Consequently, the transfer impedance can be approximated by a constant resistance even in this frequency range. The present experiment thus provides additional evidence that electrocardiographic signals, including details observed with wide-band amplifiers,[7] will not suffer frequency distortion.

For a given placement of myocardial electrodes in a patient, the transfer impedance will depend on the particular pair of surface points chosen. This transfer impedance is a *scalar* quantity, Z, which relates the voltage V in a lead to the current I injected into the myocardium. Thus $V = ZI$. Since the maximum peak voltage observed was about 6.0 mv. and the average peak current was 4.0 Ma., the maximal transfer impedance is of the order of 1.5 ohms.

A vectorial transfer impedance which is closely related but not identical to Z has been proposed by Schmitt.[8] He defines transfer impedance as a *vector* point function $\vec{Z}_u$ which relates the voltage in a lead to a current dipole moment $\vec{p}$ in the heart region as follows: $V = \vec{Z}$ [illegible] $\vec{p}$. If $\vec{d}$ is a vector joining the myocardial electrode sites and if the electrode separation is not too great, a current dipole moment, $\vec{p} = I\vec{d}$, can be associated with the pacemaker. It follows that the scalar and vectorial transfer impedances are related by $Z = \vec{Z}$ [illegible] $\vec{d}$. Since the distance between electrodes was typically 1.5 cm., and Z had a maximal value of about 1.5 ohms, vectorial transfer impedances associated with the pacemaker are of the order of 1 ohm per centimeter.

Extensive measurements of vectorial transfer impedance have been made by others using torso-shaped models filled with homogeneous conducting fluids.[8, 9] The magnitude of the impedance depends on the lead, the location of the dipole, and the resistivity of the fluid. If a value for fluid resistivity of 1,000 ohm-centimeters is used in these model studies, the vectorial transfer impedances range up to several ohms per centimeter in magnitude. It is somewhat difficult to relate our in vivo values to those obtained in model studies. The pacemaker electrodes in the epicardium constitute a dipole current source which is more ventral than the electrical center for QRS. Eccentric locations such as these should produce larger surface voltages for a given dipole moment and imply larger transfer impedance.[9] On the other hand

cardial electrodes is tangent to the intracavitary mass and on this basis, a reduction in surface voltage and transfer impedance might be anticipated.[19]

Summary

Eleven artificial pacemakers were calibrated prior to surgery. The current delivered by these units to human hearts was then measured at surgery with a current probe. Body surface pacemaker voltages were recorded subsequently in nine cases.

The amplitude and shape of the current pulse depends upon the patient load impedance. Patient load impedance consists of myocardial electrode polarization impedance and tissue resistance. For the pacemaker and myocardial electrodes employed, the patient load impedance is well represented by an equivalent circuit consisting of a series parallel arrangement of two capacitors and two resistors. Values of these circuit parameters were determined in nine cases. Tissue resistance is represented by a fraction of the series resistor in the equivalent circuit. The remainder of the equivalent circuit is attributable to polarization.

The voltage pulse measured at the body surface is related to the current pulse delivered to the myocardium by a transfer impedance. Since details of the current pulse which had a rise time of less than a microsecond were present in surface voltages, the transfer impedance is approximately resistive and independent of frequency up to a megacycle per second. It is concluded that no significant frequency distortion of electrocardiograms is caused by the electrical characteristics of body tissues.

The value of the maximal scalar transfer impedance from these studies has been cast into the vectorial form employed by others in torso model studies. Under the conditions discussed, the *vectorial* transfer impedance has comparable magnitude whether obtained from model studies or from the present pacemaker study.

Appendix

The equivalent circuit of the pacemaker connected to a resistive load R_L is shown in Fig. 3. If the switch is closed at time $t = 0$ with C_1 charged to E_o volts, then

$$I = \frac{E_o}{R_1 + R_L} e^{-t/(R_1 + R_L)C_1} \qquad (1)$$

The switch is reopened at $t = T$ seconds, producing a current pulse of duration T. During the time the switch is open, C_1 is recharged to E_o volts. E_o can be determined by observing the open-circuit voltage at the pacemaker terminals. For this measurement, the pacemaker is connected directly to the oscilloscope which has an input impedance of 10 megohms. If $(R_1 + R_L)C_1$ is greater than 5T (which was the case for the units studied), the exponential function of Equation (1) is almost indistinguishable from a straight line and a trapezoidal current pulse will be obtained. I_0 and I_T are defined as the values of I at $t = 0$ and $t = T$, respectively. Then

$$I_0 = \frac{E_o}{R_1 + R_L} \qquad (2)$$

$$I_T = I_0 e^{-T/(R_1 + R_L)C_1} \qquad (3)$$

During calibration, E_o is measured and I_0 and I_T are determined as functions of R_L. R_1 and C_1 can then be calculated from Equations (2) and (3). For the pacemakers studied, C_1 was 10 μf, R_1 with one exception was 1,600 ohms, and E_o was typically 8 volts.

Now consider that the pacemaker is connected to the load shown in Fig. 6. The pacemaker current in this case will be designated I. After the switch is closed at $t = 0$

$$I = Ae^{-t/} + Be^{-t/} \qquad (4)$$

where

$$C_T = \frac{CC_1}{C + C_1} \qquad (5)$$

$$R_T = R_1 + R \qquad (6)$$

$$R_T C_T = \frac{1 + \frac{B}{A} -}{1 + \frac{B}{A}} \tau \qquad (7)$$

$$R'C' = \frac{1 + \frac{B}{A}}{1 + \frac{B}{A} -} \qquad (8)$$

$$\frac{R}{R_T} = \frac{B}{A} \frac{(1 - -)^t}{(1 + \frac{B}{A} \frac{-}{\tau})} \qquad (9)$$

If the subscript 0 again indicates time $t = 0$

$$I_0 = A + B = \frac{E_0}{R + R} \qquad (10)$$

For the pacemakers used it was generally the case that

$$\frac{B}{A} - << 1 \qquad (11)$$

so that Equations (7) (8) and (9) simplify to

$$R_T C_T = \frac{}{1 + \frac{B}{A}} \qquad (7a)$$

$$R C' = (1 + \frac{B}{A})\tau \qquad (8a)$$

$$R = R_T \frac{B}{A} (1 - \quad -)^t \qquad (9a)$$

By plotting I as a function of t on semilog paper as described in the text it is possible to determine the parameters A B τ and τ of Equation (4) A comparison of Equations (10) and (2) shows that R is the value of R_L for which $I_0 = I_0$ and hence can be determined directly from calibration data. R_T is simply $R + R_1$ C_T is then calculated from Equation (7) or (7a) R from Equation (9) or (9a) and C' from Equation (8) or (8a) Finally C is obtained from Equation (5)

$$C = \frac{C_1 C_T}{C_1 - C_T} \qquad (12)$$

In this manner R C, R and C the parameters of the patient load equivalent circuit, are determined from A B τ and τ the parameters describing the slow portion of the current pulse delivered to the myocardium

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The elimination of respiratory signals from the ultralow-frequency ballistocardiogram

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Many time-varying physiologic signals are the net result of two or more body functions. Naturally, it is desirable to obtain "clean" signals of just one physiologic function at a time. For this purpose it is necessary to separate or filter out the unwanted signals, but complete separation is impossible by means of passive filtering if the frequency spectrums of the desired and undesired signals overlap. However, separation may be achieved by means of "active" filtering by a suitable combination of the mixed signal with another physiologic signal correlated either to the wanted signal or to the unwanted signal.

In ultralow-frequency ballistocardiography, the two main internal forces, respiratory and circulatory, give rise to displacement records, the predominant signal being that of respiration. The higher frequency circulatory component is only about 20 per cent of the amplitude of the respiratory component. It is possible to obtain a pure circulatory signal by having the subject hold his breath. However, this fixes filling of the lungs and the level of intrathoracic pressure, and the venous return and pulmonary vascular resistances are altered, producing unphysiologic circulatory conditions. What is desired is a displacement ballistocardiogram when all systems are functioning normally.

Two slightly different approaches were made in order to effect a cancellation of the respiratory component. Both methods, which involve analog computer simulations, enabled live ballistocardiographic signals to be filtered. A cancellation signal originated as a chest displacement signal which was converted by means of an analog computer into a force signal similar to the one normally produced by breathing. This signal was to be proportional to the respiratory force transmitted from the body to the bed. In the first system, this force signal fed a servo system which applied to the bed a force equal and opposite to that due to breathing; the net bed movement was then caused by cardiac forces alone. The second method was to allow free and normal displacement of the bed and to subtract a calculated respiratory displacement signal from the bed transducer

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output. This left the cardiac displacement as before. This respiratory displacement signal was calculated from the previously obtained force signal by means of an analog model of the bed

Theory

A detailed analysis of respiratory mechanics is necessary before the active filtering system can be evolved. A linear mechanical model based on the anatomy and physiology of respiration is given in Fig 1. This model is similar to the model described by Burger[1] which outlines the mechanical relationships of the cardiac forces with respect to the ballistocardiograph.

The terms outlined in Fig 1 are defined or described as follows: y = Head-foot displacement. $\dot{y}$ = Velocity in the head-foot direction. $\ddot{y}$ = Acceleration in the head-foot direction. F_1 = Internal force in the y direction due to breathing (contraction and relaxation of the diaphragm and intercostals). This force can be considered to act at the radius of a circle around an equal and opposite reaction force, F_r. M_1 = Mass of the body parts (lungs, heart, body fluids, intestine, etc.) moved directly by F_1 in a head-foot direction as a result of breathing. B_1 and K_1 = Viscous friction and spring constants of coupling of these body parts to the skeletal frame. F_r = Reaction force of the skeletal frame. M_2 = Mass of the skeletal frame plus the remainder of the body not moved directly by breathing. B_2 and K_2 = Viscous friction and spring constants of the body-to-bed coupling, i.e., skin, fat, and muscle of the back of the body which comes into direct contact with the bed. F_b = Total force transmitted from the body to the bed. F_{br} = Force transmitted from the body to the bed due to the respiratory force alone. F_{bw} = Force transmitted from the body to the bed due to the cardiac force alone. B_b and K_b = Viscous friction and spring constants of the bed-to-ground coupling system. M_b = Mass of the bed.

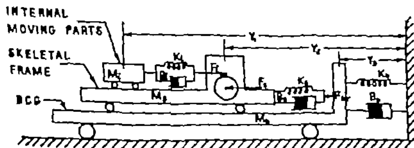
From the model of Fig 1 the force equilibrium equations (1) to (4) can be derived. From these follows

(5) $F_{bw} = -M_1\ddot{y}_1 + B_1(\dot{y}_1 - \dot{y}_2) + K_1(y_1 - y_2)$.

The tissue mass when displaced footward during respiration is redistributed and produces a proportional vertical chest and abdominal displacement which can be picked up by a suitably placed displacement transducer (see Fig 2). Therefore $Z = k_1 y_1$ and $Z = k_2 y_2$, where k_1 and k_2 are constants.

(6) $F_b = -M_r\ddot{Z} + B_r\dot{Z} + K_r Z$,

where M_r, B_r and K_r are a new set of



FORCE EQUILIBRIUM EQUATIONS

1. $M_1\ddot{Y} + B_1(\dot{Y}\ \dot{Y}_1) + K_1(Y\ Y_1) = 0$ WHERE $B_1(\dot{Y}_1 - \dot{Y}_2) + K_1(Y_1 - Y_2) = F_2$
2. $M_2\ddot{Y}_2 + B_2(\dot{Y}_2\ \dot{Y}_3) + K_2(Y_2\ Y_3) = F_3$
3. $M_b\ddot{Y}_3 + B_2(\dot{Y}_3\ \dot{Y}_2) + B_b\dot{Y}_3 + K_2(Y_3\ Y) + K_bY_3 = 0$
4. $F_{bw} = M_b\ddot{Y}_3 + B_b\dot{Y}_3 + K_bY_3 = -B_2(\dot{Y}_3 - \dot{Y}_2) - K_2(Y_3 - Y_2)$

Fig. 1. Mechanical model of system. See text.

respiratory system constants. Let the desired force signal which is applied to the ballistobed to cancel F_{br} be F'_{br}. Then

$$F'_{br} = M_r \ddot{Z} + B_r \dot{Z} + K_r Z \quad (7)$$

Details of system design

Fig. 2 outlines the two systems. Note that the total bed force F_b has been shown as the sum of the respiratory component F_{br} and the cardiac component F_{bc}.

For the first system the switch SW is in position 1. A cancellation force F'_{br} is applied directly to the bed via the servo system. If M_r, B_r, and K_r of the analog model of breathing are suitably adjusted as described later, then Equation (7) will be solved and F'_{br} will be equal to $-F_{br}$. Then F_{bc} alone will cause a bed displacement Y_c, being the desired signal.

The second system with the switch in position 2 does not employ the servo system but instead allows both F_{br} and F_{bc} to act on the bed, resulting in an unimpeded bed displacement $Y_r + Y_c$. However, the F'_{br} signal is used to produce, via an analog model of the bed, Y'_r, which if F'_{br} is properly adjusted will be equal and opposite to Y_r. Cancellation is then achieved in a differential amplifier producing Y_c as before.

The details of the equipment are as follows. (1) A Schwarzer Klensch ULF displacement BCG was used. (2) Both chest and bed displacement transducers were LVDT Sanborn Linearsyn 585 DT 050BM. (3) The servo system employed a Torque Motor MOD T2908D (Inland Motor Corporation of Virginia) coupled mechanically to the bed with a 6-inch lever arm and driven by a self-designed servo amplifier. (4) The analog model of the mechanics of respiration used standard operational amplifiers as differentiators and adders to solve Equation (7). The analog computer employed was a Heathkit Model ES400. The model of the bed likewise employed an additional group of operational amplifiers to represent the second-order model of the ballistobed.

Results and adjustments

Fig. 3 shows the results of the second of the two systems described and indicates the degree of cancellation that can be achieved. Final adjustments of M_r, B_r, and K_r were made so that a null or minimum respiratory component was seen in this net displacement record. Overcompensation resulting in too large a value of F'_{br} becomes obvious when the displacement record begins to increase again after

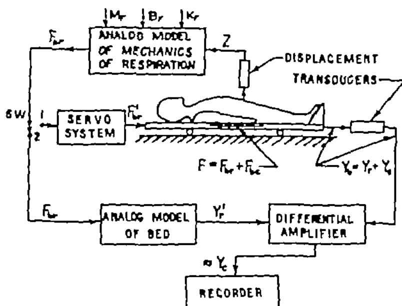


Fig. 2. Schematic diagram of systems for cancellation of respiratory component. See text.

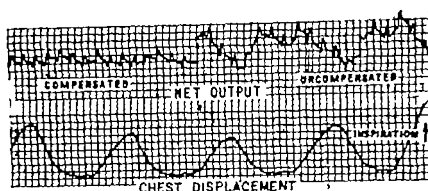


Fig. 5. Shows results of the second of the two systems described and indicates the degree of cancellation that can be achieved. See text.

passing through a null value (of Y alone). M_r, B_r, and K_r are not independent, so that any adjustment of one value requires several readjustments of the others. An optimal chest or abdominal signal must be found at a site at which minimal cardiac signals are present along with clear breathing signals in linear correlation with Y_1 and Y_2. These sites were considered to be suitable when the cardiac component was not more in amplitude than 3 per cent of the breathing signal (see Fig. 3). Suitable sites were found mostly in the lower epigastrium. Adjustments of M_r, B_r, and K_r were found to be fairly critical: a cup of coffee taken by the subject after optimal cancellation of breathing signals had been obtained upset the cancellation, indicating that the additional mass of the fluid consumed had altered M_r, B_r, or K_r.

System 2 was found to be more satisfactory mainly because of the force and frequency response limitations of the servo motor. System 1 was suitable for shallow breathing only, whereas system 2 was employed during average breathing. Both systems failed to cope with irregular or heavy breathing.

The obtained values of M, B, and K were meaningless unless given in conjunction with $\ddot{Z}$, $\dot{Z}$, and Z, which varied with the chosen site on the chest or abdomen and with the type of transducer employed. Recordings of the individual components of Equation (7) were not made. However, rough calculations indicated that the inertia force $M\ddot{Z}$ was about 80 per cent of the total force, with the viscous friction force, $B\dot{Z}$ and elastic force KZ being of comparable size and making up the balance of the total force.

Discussion

The primary problem in ultralow-frequency displacement ballistocardiography is created by the need for the subject to hold the breath during recording. This was noted as early as 1877 by Gordon[1] and it was precisely this problem which led Starr[2] to introduce his high frequency ballistocardiograph, because it is unaffected by breathing. Various attempts have been made to eliminate the respiratory effects from the ultralow frequency ballistocardiograph,[4-7] of which only one was successful, however limited in its application because of the expense involved. Previous investigations by one of us[4] have shown that it is possible to eliminate the respiratory signal from the ultralow frequency ballistocardiograph by moving a mass (Fletcher trolley) through a respirometer in the head-foot direction on the table with momentum equal, but opposite in direction, to the diaphragmatic movement. However, this increases the total mass on the bed beyond the tolerable amount for undistorted ballistocardiograms. This is why this approach involving no additional mass on the ballistobed was pursued.

One problem mentioned before is common to any such "active" filtering system. The ideal correction signal should be 100 per cent correlated with the unwanted signal and contain none of the wanted

signal Our correction signal the abdominal displacement contained a cardiac component of about 3 per cent (see Fig 3) This should produce a proportional distortion in the corrected displacement ballistocardiogram It should be possible using passive filters to eliminate most of this higher frequency cardiac component from this correction signal

Digital filtering might be employed as an alternative However this was not persued because a suitable computer was not available If such equipment were available the cost of obtaining a real time cancellation would likely be prohibitive with no guarantee of improved filtering

A useful by product of this investigation was the verification of the linear model evolved to represent the mechanics of breathing Since cancellation fails during heavy or rapid breathing it appears that nonlinearities of M B, and or K occurred in the subject

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Unipolar and bipolar stimulation thresholds of the human myocardium with chronically implanted pacemaker electrodes

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Electronic pacemaking opened up new possibilities for studying some aspects of the excitability of the human heart which are of both medical and physiologic interest.

Long term follow-up studies on stimulation thresholds in patients are few.[1-4] This report supplements the available data with observations on 11 patients over a period of 4 to 24 months. An attempt is made to answer the following questions: (1) What is the time course of the thresholds of chronically implanted electrodes? (2) What is the influence of polarity on unipolar myocardial stimulation? (3) What is the relationship, if any, between the unipolar and bipolar stimulation thresholds? (4) Is there a difference in the spread of ventricular excitation in bipolar stimulation from that in unipolar stimulation?

Methods

Thresholds were measured in 11 patients. All patients in this series were treated for total heart block by electronic pacing with an external pacemaker with surgically implanted electrodes of the type described by Elmqvist.[2] These epicardial platinum electrodes have a diameter of 9 mm.

Either 3 or 4 electrodes were implanted. The follow up period varied from 4 to 24 months.

Table I summarizes some of the relevant data.

Thresholds were measured with the aid of an external pacemaker which had a continuously adjustable amplitude and a pulse duration of 1.8 msec.† The electrocardiogram was continuously monitored and the amplitude of the current was adjusted to the minimum value which ensured 1:1 response of the heart to the pacemakers stimuli. The amplitude of the pacemaker current was then increased stepwise to two or three higher levels. At each level the output of current from the pacemaker was calculated from the difference in voltage appearing over a 100-ohm resistor in series with the patient. This voltage was measured on one channel of a dual-beam oscilloscope. The voltage appearing over the patient was measured synchronously on the second channel. At each of three amplitudes of stimulus current a high frequency four-channel electrocardiogram‡ was registered, three standard leads and one precordial lead being chosen for the comparison of the pattern of ventricular activation at different stimulus strengths.

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†Medtronic external pacemaker type 5880.
‡Mingograph Cardirex 42 B.

Table I

Patient	*Age* (yr.)	*Sex*	*Electrodes implanted* (*number*)	*Observation period* (*mo.*)
M B	67	F	3	22
S B	51	M	3	20
B V	76	M	3	16
H B	73	M	3	12
E B	48	F	3	4
M K	49	M	4	24
M C	70	M	4	18
V K	69	M	4	15
K D	65	F	4	14
M H	62	F	4	13
J V	75	M	4	7

Each electrode was used as a bipolar electrode in combination with each of the other epicardial electrodes. Furthermore, each electrode was used as a unipolar electrode in combination with an indifferent electrode, i.e., a needle in the subcutaneous tissue of the thigh or the abdominal wall. Thresholds were measured with both positive and negative stimuli in all combinations of electrodes.

On the basis of the results of measurements of threshold levels made by three independent observers no systematic interobserver differences could be found. The experimental error was then determined from 48 measurements on 12 combinations of electrodes by three different observers. The standard deviation was 0.5 milliamperes (Ma.) (i.e., the 95 per cent confidence limits of the measurement are ± 1 Ma.). Because the heart rate proved to have some influence on the ventricular threshold, all thresholds were measured at a paced rate of 70 to 80 per minute.

Results

1. Time course of the threshold in chronically implanted electrodes. This is summarized in Fig. 1. In 8 patients the threshold was measured during the implantation of the electrodes. With this type of electrode the mean preoperative threshold was 2 Ma. for unipolar stimulation with negative pulses. It rose in the postoperative period to a mean value of 6 Ma.

In 23 electrodes the threshold remained constantly at or below 7 Ma. In 5 electrodes the threshold was high in the immediate postoperative period but decreased to 7 Ma. or less in the course of the observation. In 6 electrodes the threshold rose to values above 15 Ma., which is the maximum output of current for most implanted pacemakers.

There is an indication ($p < 0.05$) that all the electrodes in a patient show a similar time course in threshold behavior. The reason for this is clear in at least 2 of our patients, S.B. and M.K., who got an ascending purulent infection around the wires, with gradually increasing thresholds until high levels were reached. None of these wires appeared to be broken, as judged from the measurements of impedance and the x-ray films.[4]

2. Influence of polarity on unipolar myocardial stimulation threshold. In Fig. 2 the unipolar stimulation thresholds for negative stimuli are plotted against the unipolar thresholds for positive stimuli for each of 39 electrodes during 25 sessions in 11 patients.

The correlation between positive and negative stimulation thresholds is high ($r = 0.9$). Therefore, the threshold to positive stimuli can be calculated with reasonable accuracy from the regression line $(y-\alpha) = \beta\,(x-\bar{x})$. The mean value $\bar{x}$ for the negative thresholds was 8.23. The 95 per cent confidence limits for α were 9.7 and 10.1. Those for the slope β were 0.98 and 1.04.

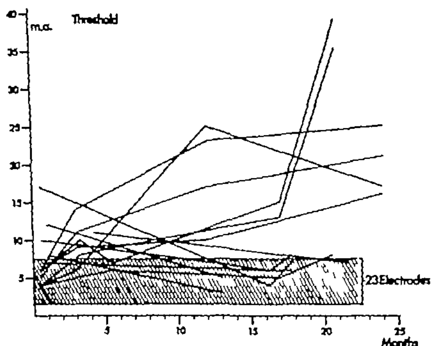


Fig. 1. Time course of thresholds for negative unipolar stimuli.

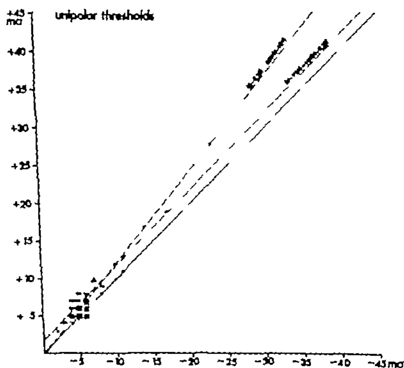


Fig. 2. Scatter diagram plotting the unipolar thresholds for positive versus negative stimuli for each measurement in each electrode.

If the positive threshold is known the negative threshold can be estimated from $(x\ \gamma) = \Delta\ (x\ \hat{y})$ The mean value $\hat{y}$ for the positive thresholds was 9 89 The 95 per cent confidence limits for γ range from 8 to 8 5 and those for Δ range from 0 77 to 0 85 The measurements in Fig 2 support the opinion that the human heart has a lower threshold for negative than for positive stimuli ($p < 0.05$) There are however some exceptions to this rule In 3 electrodes careful re-examination and comparison showed that the threshold was lower for positive than for negative stimuli.

3 Relationship between unipolar and bipolar stimulation thresholds In patients with 3 implanted electrodes and 1 indifferent subcutaneous test electrode using both polarities there are 12 possible combinations by which the heart can be stimulated In patients with 4 implanted electrodes the number of possible combinations is 20

Table II contains a representative series of measurements of thresholds one from each patient The results show the same general trend which can be summarized as follows when the indifferent electrode is used i e when stimulation is unipolar the threshold is higher than when bipolar stimulation is applied The averages of all measurements of unipolar and of bipolar thresholds are 7 4 and 5 8 Ma respectively They are statistically different ($p < 0.05$)

This difference however is not caused by some special favorable influence of the bipolar mode of stimulation on the excitability of the myocardium per se Generally the negative electrode has the lower threshold of a pair of electrodes. In this case the threshold of the pair of electrodes is determined by the unipolar threshold of the negative electrode In some pairs of electrodes however the positive electrode has the lower unipolar threshold The threshold of the pair of electrodes is then

Table II Threshold values in milliamperes of all the possible combinations of electrodes and polarities in 11 patients

Patient E B

	+Ind	+1	+2	+3
−Ind		10	8	6
−1	5		5	5
−2	5	5		5
−3	4	4	4	

Patient B V

	+Ind	+1	+2	+3
−Ind		3	5	5
−1	2		2	2
−2	4	3		4
−3	5	4	5	

Patient S B

	+Ind	+1	+2	+3
−Ind		10	17	1
−1	5		6	5
−2	8	8		8
−3	10	10	9	

Patient M B

	+Ind	+1	+2	+3
−Ind		10	7	10
−1	7		6	7
−2	4	4		4
−3	6	5	6	

Patient H B

	+Ind	+1	+2	+3
−Ind		6	5	7
−1	5		5	6
−2	6	7		6
−3	6	6	5	–

Patient M C

	+Ind	+1	+2	+3	+4
−Ind		28	12	10	7
−1	17		12	12	7
−2	7	6		6	7
−3	10	10	10		8
−4	5	5	5	5	

Patient M H

	+Ind	+1	+2	+3	+4
−Ind	–	6	19	6	8
−1	6	–	5	5	5
−2	12	6		6	7
−3	6	6	6		6
−4	8	6	7	6	

Patient J V

	+Ind	+1	+2	+3	+4
−Ind	–	10	10	10	10
−1	7	–	6	6	6
−2	12	10		10	10
−3	9	9	11	–	9
−4	13	10	10	10	–

Patient K D

	+Ind	+1	+2	+3	+4
−Ind	–	5	4	5	5
−1	6	–	4	4	5
−2	4	4	–	4	4
−3	4	4	4	–	4
−4	5	4	4	4	

Patient A K

	+Ind	+1	+2	+3	+4
−Ind		7	4	5	5
−1	6	–	5	6	4
−2	6	6	–	5	5
−3	5	5	4	–	4
−4	5	4	5	5	–

Patient M K

	+Ind	+1	+2	+3	+4
−Ind	–	6	6	8	3
−1	6	–	5	5	3
−2	5	5	–	5	3
−3	6	6	6	–	3
−4	4	3	3	3	–

Numbers 1 through 4 indicate the electrodes the polarity is indicated with the sign. Electrode combinations in which the indifferent electrode (*Ind*) is used are unipolar

determined by the unipolar threshold of the positive electrode.

It is possible therefore, to predict the threshold of each bipolar combination from the determinations of the unipolar thresholds of each of the electrodes constituting this pair

With the method of stimulation used in this study bipolar stimulation gives lower average thresholds than does unipolar stimulation simply because the measurements of threshold by nature always select the lowest from two figures.

4 Influence of the mode of stimulation on the initiation and spread of ventricular activation The observation that bipolar stimulation thresholds depend on the properties of each individual electrode raises the question whether bipolar stimuli excite the heart at one or both electrodes. The surface electrocardiogram was used as a means to judge the pattern of activation in our patients. If the amplitude of unipolar stimulation was increased from threshold level to more than 15 Ma. no change in the pattern of activation occurred in any electrode in any patient. In bipolar stimulation however the configuration of the ventricular complexes was clearly dependent on the amplitude of stimulation in at least one pair of electrodes in 10 patients. If the amplitude of the stimuli had an intensity between the unipolar thresholds of both electrodes of a given combination the ventricular complexes were comparable to those which could be produced by unipolar stimulation from the electrode with the lower threshold If the amplitude of the stimuli was increased to a level above the thresholds at both electrodes, a change in outline occurred

By a careful adjustment of the level of stimulation near the highest threshold it was sometimes possible to get an alternation of both forms of the ventricular complex in a single record In 3 cases in which the thresholds of both electrodes of a pair were almost equal three different types of ventricular complexes could be seen to alternate These were interpreted as patterns of activation from each electrode and their fusion beats (Fig 3)

Discussion

Only a few reports are available on long term observations on myocardial thresholds in patients Elmqvist[3] and Landegren[2] did follow-up studies over an average period of 6 months in 11 patients. Using

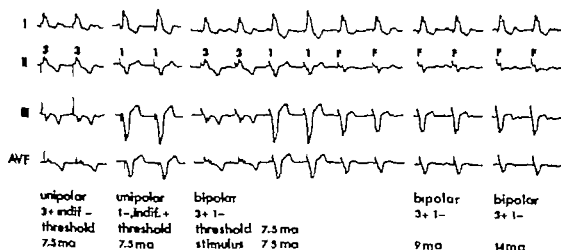


Fig. 3 Four-channel electrocardiogram obtained with different modes of stimulation of a pair of electrodes, 1 and 3 having the same threshold 7.5 Ma Unipolar stimulation of electrodes 3 (positive) and 1 (negative) gives different patterns of activation Bipolar stimulation of electrodes 3+ 1– with 7.5 Ma gives three different complexes resembling respectively the pattern of activation from electrode 3 and electrode 1 and their fusion beats, F Bipolar stimulation with 9 and 14 Ma produces fusion beats only

the same electrode as in the present study they found somewhat higher thresholds. In 9 of their 11 patients the thresholds rose above 8 Ma. In 4 patients, thresholds above 15 Ma were reached. Our data confirm the observation in these and similar studies[1-4] that the threshold tends to stabilize after an initial postoperative rise to a level well within the range of output of most commercially available pacemakers. In view of the many reports on wire breakage, it seems to be noteworthy that in 39 electrodes implanted over a total of 495 wire months not a single wire or electrode broke.

But even in intact electrodes the threshold may rise beyond the range of output of the pacemaker. In our patients, as in those of others[1,2] purulent infection around the wires was one of the main causes for the rise in threshold. Our observations show that the rise in threshold is by no means always irreversible. It appears from Fig. 1 that an early postoperative rise in threshold carries a more favorable prognosis than does a rise in threshold which occurs in later months.

To our knowledge, no studies of patients are available in which all combinations of unipolar and bipolar stimulation were systematically applied. Race and co-workers[6] reported a series of such measurements in acute experiments in dogs. It is generally accepted[6,7] that the end-diastolic threshold for negative unipolar stimuli in the heart is lower than that for positive unipolar stimuli. No quantitative data on this relationship in chronically implanted electrodes could be found in the literature. It appears that the correlation between thresholds for positive and negative stimuli is high, so that a useful estimate is obtained by means of the two regression equations or by applying a simple rule of thumb stating that the threshold for negative stimuli at each electrode is 15 per cent lower than that for positive stimuli.

We have at present no explanation for the instances observed in this study in which the threshold for negative stimuli was higher than that for positive stimuli. Conceivably, deterioration of the myocardial fibers under the implanted electrode might be responsible for this paradoxical behavior. The observation that bipolar stimulation thresholds are lower than unipolar thresholds[4,10,11] has been explained by a more favorable course of lines of current through the myocardium when the bipolar mode of stimulation is used.[10,11] With the spatial arrangement and type of electrode used in the present study this phenomenon was found to be due to the fact that in bipolar stimulation the threshold is determined by the lower of two unipolar thresholds. This conclusion does not necessarily apply to other types of bipolar electrodes for which similar studies are lacking.

Van Dam and co-workers[1,2] found in acute experiments in dogs that bipolar stimulation of the heart with currents above threshold level caused bifocal activation. A front of activation is initiated both at the anode and at the cathode. These fronts meet and merge. A similar mechanism is probably active in most patients treated with pacemakers with bipolar electrodes. Possible theoretical misgivings about the safety of continued synchronous bifocal stimulation of the human heart have in the meantime been eliminated by abundant clinical experience with this type of therapy.

Summary

Unipolar and bipolar thresholds were studied in 11 patients with 39 chronically implanted epicardial electrodes. The mode of activation at different stimulus strengths was studied electrocardiographically. The time course of threshold values over an observation period up to 24 months is described.

Regression equations are given for the threshold relationship between positive and negative unipolar stimuli. Since the correlation is high, a practically useful estimate can be obtained by means of these equations or by the simplified statement that in each electrode the threshold for negative stimuli is 15 per cent lower than that for positive stimuli. However, in some chronically implanted electrodes the threshold for positive stimuli was lower than that for negative stimuli.

Bipolar thresholds of a pair of electrodes were shown to be determined by the lowest unipolar thresholds of each of the two electrodes constituting this pair. Bipolar

stimulation with stimuli well above the threshold level will often cause bifocal activation of the human heart.

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Experimental Coxsackie virus B_4 valvulitis in cynomolgus monkeys

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Although it is known that many viruses produce myocarditis and pericarditis in man,[1-5] endocarditis is not generally considered to be a complication of viral infection.[6] Studies in this laboratory have shown that mural and valvular endocarditis can be produced consistently in mice with Coxsackie virus B_4.[7] Because of the implications of these findings relative to the etiology of valvular heart disease in man, the present study in which Coxsackie virus infection was induced in primates (cynomolgus monkeys) was performed. This paper describes the valvular lesions produced in cynomolgus monkeys with Coxsackie virus B_4.

Material and methods

Virus stock. The Coxsackie virus B_4 used in these experiments was originally recovered in 1958 by Kibrick and Benirschke from a 10-day-old infant who died of encephalohepatomyocarditis.[8] The virus obtained as monkey kidney culture passage strain was prepared in rhesus monkey kidney culture.[9] Control fluid from virus-free monkey kidney culture was also obtained. Virus and control fluid was stored at $-65°C$.

Monkeys. Nine young adult cynomolgus monkeys were obtained from Asiatic Animal Imports, San Francisco, California.

Inoculation of virus and collection of tissue. Seven monkeys were inoculated intravenously with 0.3 ml. of monkey kidney culture fluid containing Coxsackie virus B_4 $10^5 TCID_{50}$. The monkeys were killed 51 to 200 days after inoculation.

Control experiments. Two monkeys were inoculated intravenously with 0.3 *ml.* of virus-free monkey kidney culture fluid. One monkey was killed 51 days after inoculation and the other, 231 days after inoculation.

Histologic studies. Serial sections of pericardium, heart muscle, endocardium, and valves were stained with hematoxylin and eosin.

Direct fluorescent antibody staining[10] was used to identify viral antigen in the tissues in 3 of the virus-infected animals and in 1 of the control animals.

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Results

Valvulitis was found in 6 of the 7 monkeys inoculated with Coxsackie virus B_4 and in neither of the 2 control animals (Table I). Grossly, the lesions consisted of (1) verrucous aortic valvulitis in 2 monkeys, (2) verrucous mitral valvulitis in 3 monkeys (Fig. 1), and (3) cicatricial thickening of the mitral valve leaflets and chordae tendineae with commissural adhesions (stenosis) in 2 monkeys (Fig. 2).

Table I. Valve lesions in cynomolgus monkeys inoculated with Coxsackie virus B_4

*Animal number**	*Days infected*	*Valve lesion*
1	31	Verrucous lesion of mitral valve
2.	51	Verrucous lesion of aortic valve
5.	74	Verrucous lesions of aortic and mitral valve
6.	178	Verrucous lesion of mitral valve
7	185	Thick, scarred mitral valve with commissural adhesions
8.	199	None
9	200	Thick, scarred mitral valve with commissural adhesions

*No valve lesions were found in control cynomolgus monkeys Nos. 3 and 4.

Histologically, the valve tissue from the infected animals displayed stromal edema, round cell infiltration, fibrocytic proliferation, increased basophilia, and swelling of endothelial cells (Figs. 3, 4, and 5).

In the 3 virus-inoculated animals in which direct fluorescent antibody staining was carried out, viral antigen was identified in the tissues (Fig. 6), whereas fluorescent antibody staining was negative in the single control animal in which this technique was employed.

Attempts to recover Coxsackie virus from the tissues of the infected animals were unsuccessful.

Discussion

Lou, Wenner, and Kamitsuka[11] using the same strain of Coxsackie virus as that employed in the present studies, found mural endocarditis in 4 and mitral valvulitis in 2, of 9 cynomolgus monkeys inoculated with the virus. The valvular lesions described by Lou and associates consisted primarily of infiltration with polymorphonuclear neutrophils and swelling of the endothelial lining cells. Although fibrocytic proliferation and commissural adhesions were not described, these workers killed the monkeys within 28 days of

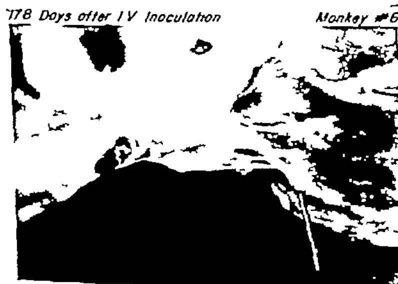


Fig. 1. Photograph showing verrucous lesion of the mitral valve associated with thickening of the [illegible] in a cynomolgus monkey inoculated with Coxsackie virus B 178 days before autopsy.

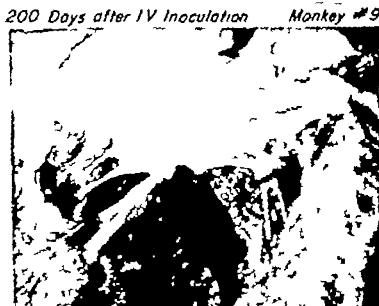


Fig 2 Photograph showing fibrosis and thickening of the mitral valve associated with commissural adhesions (stenosis) and thickening and shortening of the chordae tendineae in a cynomolgus monkey inoculated with Coxsackie virus B 200 days before autopsy

inoculation Thus, the valvular lesions observed by Lou and associates were more acute than those described in the present report. It is of particular interest that valvular lesions similar to those of human mitral stenosis with commissural adhesion and thickening and shortening of the chordae tendineae and papillary muscles were observed (Fig 2) in 2 animals in our series.

In spite of the fact that attempts to recover virus from the tissues were unsuccessful viral antigen was identified in the valves for as long as 200 days after inoculation (Fig 6)

In addition to the present studies and those of Lou and associates, viral endocarditis has been produced experimentally in mammals by Pearce[12] using Virus III in rabbits, and by Kilham Mason and Davies,[13] using encephalomyocarditis virus in mongooses. In addition Karzner[14] and Tedeschi and Stevenson[15] have described instances of valvulitis in man which were probably viral in etiology

The present studies as well as those of Lou Wenner and Kamitsuka, demonstrate that valvulitis can be produced in cynomolgus monkeys with Coxsackie virus B_4. Since Coxsackie viruses are among the most common infective agents of man[16] it would be important to know whether these viruses produce valvular lesions in man similar to those produced in monkeys Valvular lesions were not described in pathologic material from several epidemics of Coxsackie virus myocarditis among newborn infants[17,18] However in none of the infants who died during these epidemics were histologic studies of the valves described Since death usually occurred within a week to 10 days of birth sufficient time may not have elapsed to produce gross valvular lesions In adults, Coxsackie virus infection of the heart is not usually fatal so that the opportunity to study pathologic material is limited However murmurs have been described which developed during acute Coxsackie virus myocarditis and persisted long after the infection had subsided[20]

It is well known that many patients with aortic and/or mitral valvular disease give no history of rheumatic fever Nevertheless the clinician is usually satisfied to render a diagnosis of rheumatic valvulitis if no other cause of the valvular lesion can be found We think that some instances of chronic valvular disease may be due to Coxsackie virus infection. It is

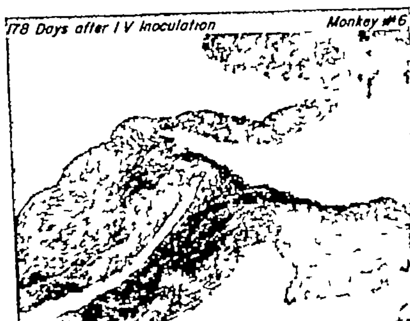


Fig 3 Photomicrograph of the mitral valve lesion shown in Fig 1 displaying round cell infiltration fibroblastic proliferation, and stromal edema.

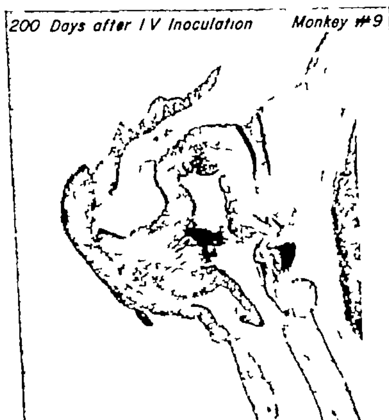


Fig 4 Photomicrograph of the mitral valve lesion shown in Fig 2 displaying round cell infiltration stromal edema and thickening of the chordae tendineae.



Fig 5 Photom rogr ph f errucous lesion f the ortic ls of ynom lgus monkey moculated with Coxsackie iru B 74 day before utopsy

Fig 6 Localization of Coxsackie virus B antigen in the mitral valve by direct immunofluorescence (X320).

also possible that other viruses in addition to Coxsackie virus may produce chronic valvular lesions in man. Inasmuch as many viruses are known to produce pericarditis and myocarditis in man there is no basis for assuming that the endocardium is resistant to viral infection. In the present studies, viral antigen was identified in the tissues by means of direct immunofluorescent techniques. This finding of course suggests direct invasion of the endocardium by the Coxsackie virus. Nevertheless, some viruses, and even Coxsackie virus, may produce endocarditis through toxicity or through an autoimmune mechanism.

Summary

Valvular lesions were found in 6 of 7 cynomolgus monkeys inoculated intravenously with Coxsackie virus B_4. Typical valvular lesions of mitral stenosis were found in 2 monkeys, verrucous aortic valvulitis was found in 2 monkeys, and verrucous mitral valvulitis was found in 3 monkeys. Viral antigen was identified in the valves of the 3 monkeys in whom fluorescent antibody staining was carried out. Valvular lesions were not found in 2 monkeys inoculated with virus-free monkey kidney culture fluid.

These studies demonstrate that Coxsackie virus produces valvular lesions in cynomolgus monkeys. Since Coxsackie viruses are among the most common infective agents of man and since a substantial number of patients with chronic valvular disease give no history of rheumatic fever, it is suggested that some instances of valvulitis in man may be due to viral rather than rheumatic disease.

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Case reports

Unusual aneurysm of the membranous interventricular septum

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Aneurysms of the membranous interventricular septum are rare and usually are not diagnosed until autopsy. Recently a patient with unusual clinical and anatomic manifestations was successfully treated by surgical excision.

Report of a case

A 57-year-old white woman, who was known to have had abnormal findings on a thoracic roentgenogram since 1956, registered at the Mayo Clinic for a general examination. When she was 20 years old, a heart murmur had been detected. Hypertension was first noted when she was in her early fifties and she was treated thereafter with a rauwolfia preparation. Specifically, she denied any distress suggesting myocardial ischemia or pleuritic chest pain, and there was no history to suggest cardiac infarction or failure.

Examination disclosed an obese woman whose blood pressure was 160 mm. Hg systolic and 96 mm. Hg diastolic. Peripheral arterial pulses were normal to palpation, as were the retinal arterioles on ophthalmoscopy. Auscultation of the heart revealed unusual findings. A systolic murmur of moderate intensity, heard maximally over the right lower sternal border, ended immediately before a normal second sound, which could be split into its components with inspiration. The second sound was followed immediately by a decrescendo murmur that occupied the first third of diastole. No other pertinent findings were detected on physical examination.

An electrocardiogram showed normal ventricular complexes with a mean QRS axis of +30 degrees. By contrast, the mean P axis was −30 degrees (Fig. 1).

Thoracic roentgenograms that had been made previously on Aug. 8, 1952, Oct. 15, 1956, and June 25, 1957, were reviewed. No definite abnormality was noted on the 1952 film. In 1956, a shadow was seen along the right cardiac border. In 1957 it had enlarged slightly. The film made at our clinic in 1964 (Fig. 2) demonstrated further enlargement of the mass. This mass was considered to be located anteriorly but could not be separated from the cardiac silhouette by roentgenoscopy.

Right cardiac catheterization showed normal pressures. Dye-dilution curves via injection into the superior vena cava, main pulmonary artery, and aortic root with sampling from the femoral artery were normal. There was no evidence of any shunt on either dye curves or oxygen saturations. An angiocardiogram via injection into the superior vena cava (Fig. 3,A) and another from the aortic root (Fig. 3,B) showed an undyed lesion along the right cardiac border displacing the right atrial appendage.

An exploratory right thoracotomy was performed, and a large pulsating aneurysm, under systemic pressure arising from the region of the heart and great vessels, was encountered. Its exact site of origin could not be determined. Resection through this incision and without the help of cardiopulmonary bypass was impossible, so that the patient underwent another thoracotomy later through a median sternotomy. The aneurysm was seen to arise from the right in the region of the base of

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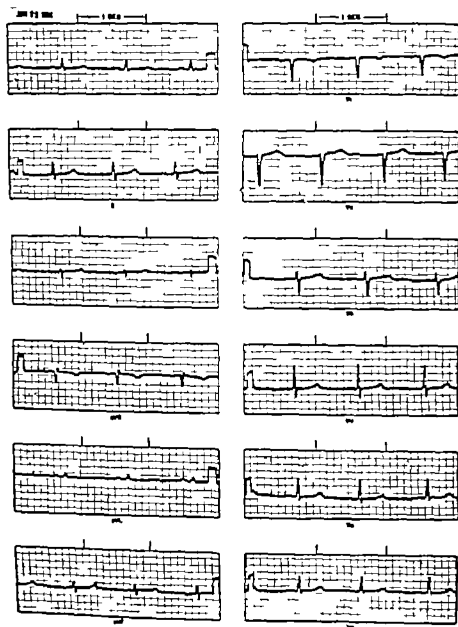


Fig. 1 Electrocardiogram showing mean P axis of −30 degrees.

the aorta, pushing the right atrium posteriorly and the right ventricle anteriorly (Fig. 4). Pulsations were synchronous with ventricular contraction, and there was a diastolic thrill at the base of the aneurysm. After extracorporeal circulation was instituted, the aneurysm was opened. It arose high in the membranous part of the interventricular septum just below the noncoronary cusp and the commissure between it and the right coronary cusp of the aortic valve (Fig. 4). It communicated only with the left ventricle through a defect of about 8 mm. in its greatest diameter. There was extensive calcification around the neck of the aneurysm as well as around its base. The bulbous portion of the aneurysm measured about 10 cm. in diameter. The major part of the aneurysm was resected and the defect was closed with mattress sutures reinforced with Teflon felt (Fig. 4, *lower inset*).

Pathologic examination revealed that the wall of the aneurysm was composed of hyaline fibrous tissue, with marked sclerosis and calcification of the endocardial surface and slight chronic inflammation of the epicardial surface. There was neither muscle nor elastic tissue in the wall.



Fig 2 Posteroanterior chest film showing shadow along right cardiac border

The patient postoperative course was uneventful. Examination prior to discharge disclosed no murmurs. Thoracic roentgenograms demonstrated minimal evidence of pleural reaction and a normal cardiac silhouette. The electrocardiogram showed only nonspecific T wave changes.

Comment

About 80 cases of congenital aneurysms of the membranous interventricular septum had been reported prior to 1955[1] In two autopsy series, the incidence was 4 in 3 000[2] and 2 in 16 000[1] respectively. In another series of 1 000 cases of congenital heart disease there were 7 isolated septal aneurysms and an additional 9 associated with other cardiac defects.[3] There was no predilection to either sex or any particular age group the ages varied from 5 months[4] to 72 years.[5]

The cause seems to be congenital[4,6] The association with mongolism[6] as well as with other cardiac defects,[8] such as ventricular septal defect[4,3,11] malformation of the pulmonary or aortic valve[12] especially with aortic insufficiency[12-13] corrected transposition[15] or atrioventricular canal[7,16] has been described. One patient had associated hemangiomatous capillary invasion of the pulmonary arterioles leading to cor pulmonale.[17] Our patient had no evidence clinically by special studies, or at operation of any acquired heart disease to explain the aneurysm and there were no associated congenital cardiac defects. The murmur had been present at least 25 years, and in all probability this aneurysm was an isolated congenital anomaly.



Fig 3 A Angiocardiogram from the superior vena cava showing filling of the latter the right atrium and its appendage right ventricle and pulmonary artery but no filling of the shadow along the right cardiac border. *B* Aortic-root angiogram. No filling of the mass occurs.

Aneurysms of the membranous interventricular septum are considered to be a result of a basic abnormality in the development of the endocardial cushions.[7] Mall[8] in 1912 proposed that this may be due to lack of sufficient shifting of the

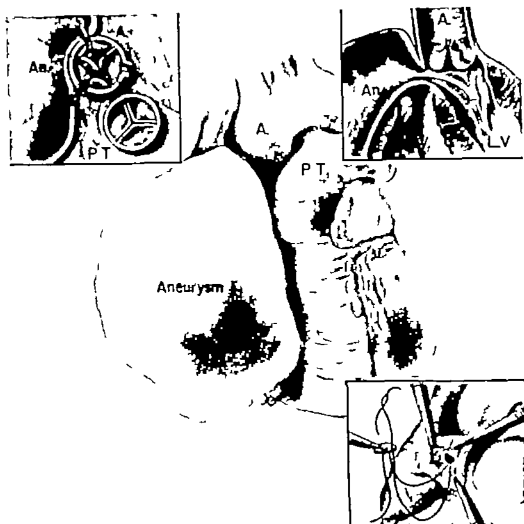


Fig. 4. Drawing of aneurysm as it appeared at operation. Upper left inset demonstrates the relationship of the aneurysm to the aortic valve as viewed from above. Dotted line indicates site of sagittal section depicted in upper right inset. Lower inset demonstrates appearance of the section of the aneurysm. The technique of repair is shown. *A*, Aorta. *An*, Aneurysm. *LV*, Left ventricle. *RV*, Right ventricle. *PT*, Pulmonary trunk. Arrows pass from the left ventricular outflow tract into the aneurysm, showing the communication between the two

aorta to the left and of the septum to the right during cardiogenesis, and therefore, the membranous septum comes to lie more horizontally or obliquely than normal this abnormal position renders it weaker and more susceptible to the formation of an aneurysm Lev and Saphir[4] proposed the same hypothesis, and they even went so far as to call the condition a mild form of transposition.

Anatomically the usual site of origin of the aneurysm seems to be the region of the commissure between the right coronary and noncoronary cusp[12,13,14-15]

Because of differences in pressure, these aneurysms usually pouch into the right sides of the heart,[2,4,5,6,8,11,15-17,19] either into the right atrium at the tricuspid valve itself or into the right ventricle In 3 cases associated with a ventricular septal defect, the aneurysm was believed to have produced obstruction of the right ventricular outflow tract[8,11,12] and in one case, of the left ventricular outflow tract.[20]

Presentation of a septal aneurysm outside the heart is indeed rare. We have been able to find only 3 cases reported and this condition was found at autopsy One

case[17] was that of a 37 year-old man who had an aneurysm that arose in the posterior wall of the aortic vestibule and communicated with an extracardiac cavity that had ruptured causing the patient's death There was an associated bicuspid aortic valve and a single coronary ostium as well as bacterial endocarditis of the region of the aneurysm which may have contributed to its rupture The second case[11] was that of a 39-year-old woman who had a defect below the noncoronary aortic cusp leading to an aneurysm that burrowed its way between the pulmonary artery and the left atrium There was also fenestration of the right aortic cusp with aortic insufficiency The third case[18] was that of a 2 year-old boy who had an aneurysm presenting between the pulmonary trunk and aorta and right atrium In none of these cases did the aneurysm approach the size of that in our case nor did it extend as far beyond the cardiac silhouette

It has been stated that aneurysms of the membranous interventricular septum usually are not of any clinical significance[7,13] In some of the reported cases the aneurysm has been an incidental finding at autopsy in an asymptomatic individual[6,9,16] in others the clinical picture was dominated by the associated defect[2,3,4,8,11,13,1,17,18] On the other hand in other reports the aneurysm was the major cause of morbidity or death In one case[17] the aneurysm ruptured leading to hemopericardium and death from tamponade Rupture into the right side of the heart leading to a left-to-right shunt and the formation of thrombi or bacterial endocarditis also have been described[14] Right bundle branch block,[16] various supraventricular arrhythmias,[3,7,15] ventricular tachycardia complete atrioventricular block with Stokes-Adams attacks, and sudden death[19] also have been reported Our patient had no symptoms referable to the cardiovascular system at any time, in spite of the huge size of the aneurysm Perhaps this may have been due to its extracardiac presentation.

A systolic murmur and an early decrescendo diastolic murmur associated with an aneurysm of the membranous ventricular septum have not, to our knowledge been previously described although these murmurs were reported in 5 of 20 cases of aneurysms of the myocardial wall itself[21] That these murmurs should occur with a septal aneurysm does not seem to be unusual since the same pressure relationships between the left ventricle and the aneurysm prevail throughout the cardiac cycle

The diagnosis of this condition has, in the past usually been made at autopsy[2,4,6,8,9,12,13,14,16,19] Schumacher and Clover[19] reported the case of a 12 year-old boy with a ventricular septal defect in whom a left ventriculogram demonstrated a septal aneurysm bulging into the right ventricle The aneurysm was successfully excised at the same time that the ventricular septal defect was closed Three similar cases were reported—1 by Terasillo and associates[5] and 2 by Das and co-workers[11]—although in these the aneurysm was not noted before the operation The other cases of septal aneurysm in which a clinical diagnosis was made were reported by Steinberg[1] Lekisch[22] and Campbell and associates[23] In all instances, the diagnosis was made by angiocardiography during cardiac investigation of cardiomegaly in 1 case and an asymptomatic systolic murmur in the other 2 cases All of these cases however lack surgical or pathologic confirmation An excellent review by Baron and associates[1] of the angiocardiographic features of aneurysms of the membranous septum has been published recently

The ventricular septal aneurysm in the case reported herein was not recognized before operation Because of the murmur a communication from either the aorta or coronary artery to a chamber of the right side of the heart resulting in a left to-right shunt was considered Because of the radiographic findings, aneurysmal dilatation of either the right atrium coronary sinus or coronary artery was believed to be present These diagnostic considerations seemed to be excluded by the study In retrospect however the diagnosis could have been made angiocardiographically if serial filming which would have shown filling of the left ventricle had been continued

Another unusual finding was the abnormal P wave vector of -30 degrees, which was presumably due to displace-

ment of the right atrium and sinus node by the aneurysm.

Summary

The case of a patient with a huge aneurysm of the membranous interventricular septum is presented This is believed to be the first such patient without associated anomalies to have undergone successful resection

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Persistent atrioventricular dissociation with block and nodal rhythm after cardiac catheterization

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Transient atrioventricular (A-V) block is not uncommonly observed during cardiac catheterization as a result of manipulation of the catheter within the cardiac chambers. Indeed, in a large series of catheterizations in children recently reported by Black and his co-workers,[1] 4.3 per cent of the studies were complicated by second- or third-degree A-V block. These authors noted, however, that it was unusual for the arrhythmia to persist for more than 1 hour, and in no instance was the block sustained for more than 5 days. Moreover, we have encountered no reports of persistent A-V block resulting from cardiac catheterization.

The present report describes a patient with cyanotic congenital heart disease in whom A-V dissociation with block and a slow nodal rhythm developed abruptly during cardiac catheterization. The arrhythmia persisted and required the implantation of a permanent pacemaker 9 months after its onset.

Case report

D. D., an 8-year-old white female, was first admitted to the National Heart Institute in 1958 for the evaluation of cyanotic congenital heart disease. Cyanosis and a heart murmur had been noted at birth, and she subsequently exhibited poor growth, squatting, fatigue with exertion, and increasing polycythemia. On physical examination, the blood pressure was 120/100 mm. Hg, the pulse was 96, and respirations were 24 per minute. There was moderate cyanosis and prominent digital clubbing. Dullness to percussion, with decreased breath sounds and absent tactile fremitus, was elicited over the right hemithorax. The left side of the chest was clear. A right parasternal systolic heave was present. There was a Grade 3/6 ejection murmur loudest along the right sternal edge. The second sound was single. Gastric tympany was detected in the left hypochondrium. The liver and spleen were not palpable, and there was no edema. The patient was below the third percentile in both height and weight. The hematocrit was 78 per cent. On chest x-ray examination, the heart lay entirely within the right hemithorax; no right pulmonary markings were present. The electrocardiogram was interpreted as showing normal sinus rhythm, a P-R interval of 0.16 second, and a mean spatial P axis of +150 degrees. The mean QRS axis was +105 degrees, and the QRS configuration suggested right ventricular hypertrophy. Right heart catheterization demonstrated valvular and infundibular pulmonary stenosis, and ventricular septal defect (tetralogy of Fallot), with equal right and left ventricular pressures, predominant right-to-left shunt, and arterial oxygen unsaturation (77.3 per cent). Right ventricular angiocardiography revealed dextroposition of the heart, with agenesis of the right pulmonary artery and right lung. A subclavian-pulmonary arterial anastomosis was recommended, but the family elected to postpone operation. Digoxin, 0.2 mg. daily, was initiated with no change in P wave configuration or P-R interval.

In December, 1962, when the patient was 11

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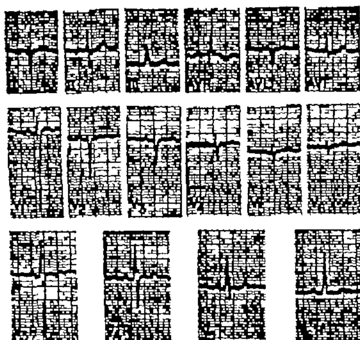


Fig. 1. Electrocardiogram recorded prior to postoperative cardiac catheterization. The tracing was interpreted as showing normal sinus rhythm and right ventricular hypertrophy in the presence of cardiac dextroposition. Time lines, 0.04 second; paper speed, 25 mm. per second.

years old, pulmonary valvulotomy was performed because of increasing cyanosis and dyspnea. At thoracotomy the heart was found to occupy the entire right hemithorax, the atria exhibited a normal anatomic relationship, and the right ventricle was markedly enlarged. The right ventricle comprised the entire anterior surface of the heart, and lay to the right of the left ventricle.

Pulmonary valvulotomy resulted in distinct benefit, but within 8 months the patient's symptoms returned, prompting her third admission to the National Heart Institute in December, 1963. The hematocrit was 51 per cent. The arterial oxygen saturation was 77.5 per cent with the patient breathing room air. No increase in left pulmonary vascularity was apparent on the chest x-ray film. The electrocardiogram (Fig. 1), as before, showed sinus rhythm with a P-R interval of 0.16 second, and a mean P axis of approximately +150 degrees (see electrocardiographic interpretation). The mean QRS axis had shifted further rightward to +135 degrees. On Feb. 25, 1964, a cardiac catheterization was performed. The simultaneous right ventricular and femoral arterial pressures were 108/4 and 106/64 mm. Hg, respectively. The catheter crossed a high ventricular septal defect and entered the aorta. As the tip of the catheter was withdrawn from the aorta to the right ventricle, the cardiac rhythm reverted abruptly from a sinus mechanism (Fig. 2, *A-1*) to the pattern illustrated in Fig. 2 *A-2*, interpreted as nodal rhythm with incomplete A-V dissociation with block, and occasional ventricular capture by the sinus pacemaker (see electrocardiographic interpretation).

Digitalis was discontinued, and attempts were made to re-establish a conducted sinus rhythm with atropine and isoproterenol. The arrhythmia was unchanged by these maneuvers, and it persisted despite a 10-day course of prednisone, 40 mg. daily, and hydrochlorothiazide, 50 mg. daily. The ventricular rate ranged from 50 to 56 per minute. Accordingly, digitalis was reinstituted, and the patient was discharged. The electrocardiogram at the time of discharge is illustrated in Fig. 2,*B*.

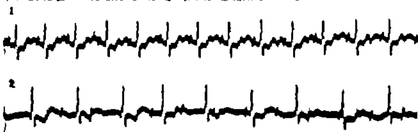
Over the ensuing months there was a progressive and marked increase in dyspnea, fatigue, and cyanosis. The heart rate of 50 to 60 per minute persisted and, therefore, in December, 1964, 9 months after the onset of the arrhythmia, a permanent ventricular pacemaker was implanted.* Pressures (mm. Hg) recorded during this operation were: pulmonary artery, 48/9; right ventricular infundibulum, 31/9; right ventricular body, 92/9; brachial artery, 106/83. Electrocardiographic tracings recorded prior to operation are shown in *C* and *D* of Fig. 2.

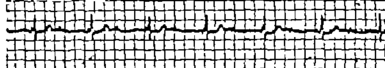
The patient sustained moderate symptomatic improvement with the increased ventricular rate induced by the pacemaker. An electrocardiogram obtained on a subsequent admission (February, 1965) for pacemaker failure revealed no change in the arrhythmia.

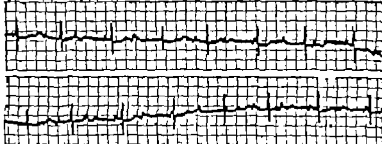
Electrocardiographic interpretations

The interpretation of the arrhythmia exhibited by this patient is complicated by

*Medtronic, Inc., Minneapolis, Minn. Model 5821-A.







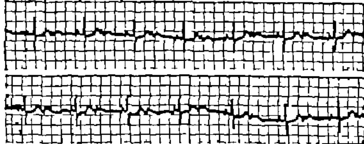


Fig. 2. Electrocardiographic tracings recorded immediately before and at intervals following development of the arrhythmia. *A-1*. Lead II taken during cardiac catheterization showing normal sinus rhythm. *A-2*. Lead II taken immediately after withdrawal of the tip of the catheter from the aorta to the right ventricle, showing incomplete A-V dissociation A-V block, with nodal rhythm. *B*. Lead II taken 3 weeks after onset of the arrhythmia showing persistent incomplete A-V dissociation with block, and nodal rhythm. *C* and *D*. Lead II taken 9 months after onset of the arrhythmia: no change in the arrhythmia is apparent. Time lines, 0.04 second paper speed, 25 mm. per second.

the presence of anatomically proved cardiac dextroposition and an unusual P wave contour. The tracing illustrated in Fig. 1 taken prior to the onset of the arrhythmia shows the pattern of atrial depolarization consistently recorded over the 8-year period of observation. The manifest atrial mean electrical axis of approximately +150 degrees can be considered to be compatible with a sinus mechanism in the presence of dextroposition (and dextrorotation); right atrial enlargement may also contribute to its rightward orientation.[8] The anteroinferior orientation of the mean atrial electrical axis is most compatible with a sinus, rather than an ectopic, origin

of the atrial rhythm[1,2] It was also noted that, during typical episodes of wandering supraventricular pacemaker slowing of the atrial rate was accompanied by a slight shortening of the P R interval (from 0 16 to 0 15 second) and a change in mean atrial electrical axis to −165 degrees directed slightly posteriorly

The QRS morphology (Fig 1) interpreted in the light of cardiac dextroposition was considered to be consistent with right ventricular hypertrophy[2]

Fig 2 demonstrates the sequence of electrocardiographic tracings obtained at the onset of the arrhythmia and over the ensuing 9 months prior to insertion of the pacemaker

Fig 2,*A 1* Lead II taken at the beginning of cardiac catheterization on Feb 25 1964 shows normal sinus rhythm at a rate of 92 per minute. The P R interval is 0 16 second Lead II is illustrated in Fig 2,*A 2* immediately after the catheter was withdrawn from the aorta, across the ventricular septal defect into the right ventricle. This tracing reveals a regular sinus pacemaker at a rate of 95 to 100 per minute, with incomplete A V dissociation A V block and a nodal rhythm at a rate of 63 per minute (R R interval 0 91 0 95 second) Ventricular capture occurs with the fourth QRS after a shorter R R interval (0.80 second) The R P interval for the P wave preceding this beat is 0.58 second P waves which follow ventricular depolarizations by 0.50 to 0.56 second are not conducted Note that the fifth QRS also terminates a shorter R R interval (0 87 second) The R P interval for the preceding P wave is only 0.38 second Since the other beats of A-V nodal origin are somewhat irregular it is possible that the shorter cycle terminated by the fifth ventricular beat is simply a manifestation of this irregularity Review of the available tracings taken at this time reveals this to be an isolated phenomenon and suggests that this does not represent supernormal phase conduction The slight difference in QRS morphology e.g the sixth as compared with the seventh ventricular complex, is apparently not related to ventricular aberration of nodal beats, since both QRS forms are seen with nodal beats.

The tracing shown in Fig 2,*B* was taken at the time of discharge of the patient from the hospital March 19 1964 A regular sinus pacemaker is again noted now with complete A V dissociation A V block, and a nodal rhythm with a ventricular rate of 52 per minute It is difficult to assess accurately the degree of A V block here by virtue of isorhythmic dissociation It is unlikely that concealed conduction of alternate sinus impulses accounts for the relatively slow nodal rhythm since the R R interval remains almost constant in the presence of a changing P-QRS relationship

Because of clinical deterioration with a continued slow ventricular rate the patient was re-evaluated in November 1964 and the electrocardiogram at that time (Fig 2,*C* and *D*) revealed the arrhythmia to be essentially unchanged In Fig 2 *C* the sinus rhythm is regular at a rate of 105 to 110 per minute whereas the ventricular rhythm is irregular with a predominant R R interval of 1 00 second The second fifth seventh, tenth and fourteenth QRS complexes represent ventricular capture by the sinus pacemaker The P R intervals for these beats range from 0.26 to 0 45 second and vary inversely with the length of the antecedent R P interval When a P wave follows a QRS complex by 0.54 second or more ventricular capture occurs, while those P waves with R P intervals of 0 46 second or less are not conducted In this tracing then the presence of A V block is again clearly defined

In Fig 2 *D* (November 1964) ventricular capture does not occur the ventricular rhythm is maintained by the nodal pacemaker at a rate of 56 to 60 per minute similar to the nodal rate in Fig 2 *C* The somewhat faster atrial rate (110 to 118 per minute) as compared with the tracing in Fig 2 *C* resulting in isorhythmic dissociation may account for failure of ventricular capture to occur In this tracing the atrial pacemaker does not test A V conduction at a time relative to the nodal cycle which might allow a more accurate assessment of the degree of A V block.

Discussion

Although Black and associates[1] have reported an incidence of second and third degree A V block of 4.3 per cent in a large

series of procedures in children, the occurrence of A-V block during cardiac catheterization is relatively unusual. The persistence in chronic form of A-V block secondary to manipulation of the catheter within the heart has not been documented previously. In the case presented, A-V dissociation with block developed abruptly during cardiac catheterization, failed to remit, and required pacemaker implantation 9 months after onset. The patient, a child with tetralogy of Fallot, agenesis of the right lung, and cardiac dextroposition, had not evidenced A-V block over an 8-year period of observation prior to catheterization. During the procedure, as the tip of the catheter was withdrawn from the aorta across the ventricular septal defect into the right ventricle, there was the sudden onset of incomplete A-V dissociation with block and slow nodal rhythm. Attempts to establish a conducted sinus rhythm, including trials of adrenocortical steroid therapy and induced hypokalemic alkalosis, were unsuccessful. The slow ventricular rate associated with the arrhythmia appeared to be responsible for the later clinical deterioration of the patient and required the implantation of a permanent pacemaker.

It is reasonable to ascribe the abrupt onset of A-V block in this instance to trauma to the A-V conduction system. Since the tip of the catheter was recording an aortic pressure tracing at the point of onset of the arrhythmia, the only segment of the conduction system seemingly accessible to trauma from the catheter was the atrioventricular bundle, which presumably was compressed as the catheter was withdrawn across the posterior margin of the ventricular defect. Lev[4] has demonstrated that in tetralogy of Fallot the atrioventricular bundle lies near the posterior margin of the defect, although it is not so intimately related to this margin as it is in uncomplicated ventricular septal defect.[5] Black and associates[1] reported that A-V block occurred when the tip of the catheter lay within the right atrium or right ventricle, where both A-V junction and bundle of His might be traumatized. Although their study indicated that the incidence of transient A-V block during cardiac catheterization is significantly higher in certain malformations such as tetralogy of Fallot, the anatomic basis for this apparent susceptibility to catheter trauma to the conduction system in these lesions remains uncertain.

Summary

A patient is presented in whom incomplete atrioventricular (A-V) dissociation with block and slow nodal rhythm developed abruptly during diagnostic cardiac catheterization. In contrast to such instances of A-V block reported previously, the arrhythmia persisted, and a pacemaker had to be implanted 9 months after onset because of clinical deterioration associated with the accompanying slow ventricular rate.

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Review

ECG changes resulting from cerebral stimulation

II A spectrum of ventricular arrhythmias of sympathetic origin

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That electrical stimulation of the hypothalamus evokes cardiovascular changes hardly requires emphasis. More than 50 years ago Karplus and Kreidl[1] observed that electrical stimulation of this area of the brain elicited alterations in systemic blood pressure and heart rate. These findings have since been confirmed and extended by numerous investigators. In a recent review article, Hoff Kell and Carroll[2] examined a voluminous literature and assessed the influences of electrical stimulation of telencephalic, diencephalic and mesencephalic structures upon cardiovascular function. These writers concluded that, although stimulation of certain cortical and subcortical areas evoked a variety of cardiovascular changes, cortical loci appear to exert a more specific autonomic control than do lower levels of the brain Studies from our laboratories continue to lend support to this hypothesis.

Thus, although many workers have reported that stimulation of the brain produces alterations in the electrocardiographic complex, accurate description of these arrhythmias has, for the most part been wanting Furthermore much controversy has existed as to the role played by both divisions of the autonomic nervous system in the mediation of these ectopic ventricular rhythms.

In the following experiments an attempt was made to describe accurately the alterations in cardiac rhythm which were observed when mesencephalic and diencephalic structures were systematically explored with electrical stimuli of known parameters.

Methods

Twenty-five female beagle dogs weighing between 7.8 and 12.3 kilograms were used in these experiments. All animals were anesthetized with thiamylal sodium† administered intravenously The initial dose was 0.5 mg per kilogram of body weight and a light state of anesthesia was sustained with increments of 1 to 2 mg per hour

Each animal was held securely in a Kopf stereotaxic instrument. A midline incision was made in the scalp and the muscles were dissected subperiosteally from the bone. The skull was then marked and burr holes were drilled for the stimulating electrodes. All placements of electrodes were guided by the system of coordinates developed by Lim Liu and Moffitt.

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†Surital sodium, Parke, Davis and Company Detroit, Mich.

The bipolar stimulating electrode was made of Formvar-coated stainless steel wire 0.010 inch in diameter. Two pieces of this wire were straightened and twisted together in such a manner that the tips, one above the other, were separated by 1 mm., with the insulation scraped away approximately 0.5 mm. from the tips. Prior to each stimulation, tissue impedance was measured with a bridge circuit, and the stimulating current was adjusted to 1 Ma. Symmetrical biphasic pulses were delivered from 2 AEL stimulators while the constant current was monitored on a Tektronix oscilloscope. In some experiments, the stimulus intensity was progressively increased in steps of 0.5 Ma. to 2 Ma. Other parameters were identical in all experiments: 50 c.p.s. with a 1 msec. pulse width. The duration of each stimulus presentation was usually 60 seconds, but in some studies it varied from 15 to 120 seconds.

In all experiments, the electrocardiogram was recorded from Standard Lead II, and systemic blood pressure was measured with a Statham P23Dc transducer from a catheter in the femoral artery. All recordings were displayed on a Grass Model 5 six-channel direct ink writing polygraph.

Neural loci which were systematically explored included primarily the central gray substance and reticular formation of the midbrain and the ventromedial region of the hypothalamus. Table I lists the coordinates.

Table I. Coordinates of electrode placements in diencephalon and mesencephalon from which responses were elicited

Anterior to interaural line (mm.)	Lateral to midline (mm.)	Depth (mm.)
7	5.75	+9.5
8	2	+6
		+8
		+10
		+12
		+15
9	1.5	+15
	3	+10
10	3	+13
11	2	+12
13	1.5	+14
		+15
20	1.5	+6
		+7

In order to differentiate between sympathetic and parasympathetic effects on the heart, the influence mediated by either division of the autonomic nervous system was selectively eliminated. In 5 animals, cerebral loci were stimulated before and after bilateral cervical section of the vagosympathetic trunks. Furthermore, a beta adrenergic blocking agent (propranolol*) was administered intravenously (1 mg. per kilogram) to the vagotomized animals, and from 5 to 10 minutes after the injection a third train of electrical pulses was delivered to the same neural locus.

The Prussian blue method[4] permitted accurate histologic verification of placement of the electrodes.

Results

Electrical stimuli delivered to loci in the diencephalon and mesencephalon elicited a variety of ectopic ventricular rhythms.

From 5 to 20 seconds after the onset of an intense stimulus (2 Ma.), a sinus tachycardia was followed by ventricular fusion contractions, ventricular premature contractions (which were frequently multifocal and coupled to the preceding normal sinus complex, in bigeminal and trigeminal patterns), ventricular tachycardia, and in some experiments, ventricular fibrillation. At this point, termination of electrical stimulation converted the latter arrhythmia in sequence to ventricular tachycardia, ventricular premature contractions coupled to the preceding normal sinus complexes, and ventricular fusion contractions followed by a return to sinus tachycardia. Such a spectrum is illustrated in Fig. 1.

During some stimulations a bypass was observed to occur directly to ventricular fusion contractions and thence to sinus tachycardia, whereas in other instances the conversion was directly to sinus tachycardia.

In contrast, if a particular rhythm were

*Inderal, Ayerst Laboratories, Inc., New York, N. Y.

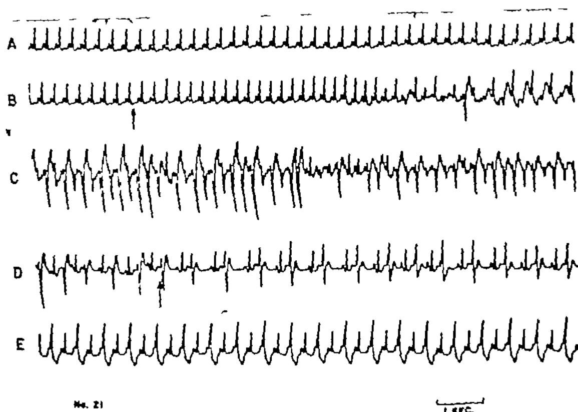


Fig. 1 A spectrum of arrhythmias elicited by electrical stimulation of a locus in the mesencephalic reticular formation. *A* Control record. *B* Arrow indicates onset of stimulation. *C*, During stimulation. *D* Arrow indicates offset of stimulus. *E*, Fusion contractions which preceded a return to sinus rhythm

evoked by an electrical stimulus delivered to a neural locus for example, sinus tachycardia, modest increments in the intensity of the stimulus would evoke, in sequence, ventricular fusion contractions, ventricular premature contractions ventricular tachycardia and ventricular fibrillation. After the latter arrhythmic complex, termination of the stimulus resulted in a reversal of the sequence just outlined It is noteworthy that these abnormal complexes maintained a distinct order in this sequence however as mentioned previously a bypass did sometimes occur and the fusion contractions would not be observed

Bilateral section of the vagosympathetic trunks had no influence upon the sequence of abnormal complexes. This is illustrated in Fig 2

It should be noted that, in this sequence, the fusion phenomena which in certain instances fulfill the criteria of the Wolff Parkinson White[5] complexes preceded the return to normal sinus rhythm A similar response was observed in different animals from most loci stimulated

From 5 to 10 minutes after the intravenous administration of propranolol in the previously vagotomized animal electrical stimulation of loci in the diencephalon and mesencephalon had no observable effect on either heart rate or rhythm. Fig 3 shows the normal sinus rhythm observed under these conditions.

In other experiments with vagotomized animals, when ventricular premature contractions were experimentally elicited all ventricular rhythm was completely abolished by immediate electrical stimulation of the distal cut-end of the right vagus. (A stimulus of sufficient intensity to produce complete arrest of the sinoatrial pacemaker was used.) This is illustrated in Fig 4.

A

B

C

D

E

F

No. 28

1 SEC.

Fig. 2. Sequence of arrhythmias in vagotomized animal evoked by electrical stimulation of the ventromedial region of the hypothalamus. *A*, Control record. *B*, Arrow indicates cessation of stimulation (60 seconds after its onset). *C*, Ventricular premature contractions followed by fusion contractions. *D*, Fusion contractions. *E*, Fusion contraction resembling Wolff-Parkinson-White complexes. *F*, Return to sinus rhythm.

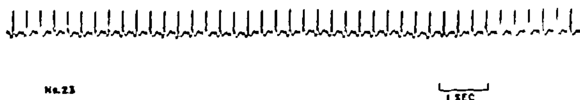


Fig. 3. Sinus rhythm recorded from vagotomized animal during electrical stimulation of ventromedial region of the hypothalamus after beta-adrenergic blockade. (Same animal as in Fig. 2.)

Discussion

A most interesting aspect of these results is the demonstration of a spectrum of ectopic ventricular rhythms in the normal heart of adult beagle dogs. It is noteworthy that each ventricular aberration occupies a distinct position on this continuum and that the specific arrhythmia observed is directly related to the intensity of sympathetic efferent discharge. Furthermore, the spectrum of ectopic complexes embraces all of the ventricular arrhythmias that are observed in the clinical situation.

In an earlier study[illegible] we had shown that ventricular fusion contractions resembling the Wolff-Parkinson-White complex were dependent upon impulses from the sino-

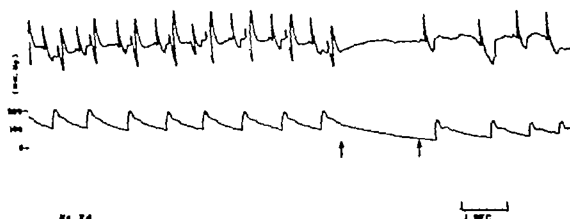


Fig. 4 Ventricular premature contractions elicited by electrical stimulation of focus in the mesencephalic reticular formation. Arrows indicate onset and off-set of stimulus to distal cut-end of right vagus.

atrial node pacemaker. In the present experiments, we have similarly demonstrated that ventricular premature contractions, observed in bigeminal patterns, are also dependent upon the same mechanism. In contrast, depression of the sinoatrial node pacemaker by electrical stimulation of the vagus nerve has no influence upon ventricular tachycardia elicited by stimulation of diencephalic and mesencephalic structures. Thus, the dependency of the ventricular rhythm upon the sinoatrial node pacemaker would appear to be closely related to the intensity of sympathetic efferent discharge to the ventricular myocardium.

In this same study[6] we had also reported that electrical stimuli delivered to a circumscribed field in the mesencephalon produced alternating WPW-like complexes. Although other arrhythmias had been observed in these experiments, a precise analysis of these complexes was not carried out. It is indeed obvious from the studies which we are now reporting that the WPW-like phenomenon lies on a continuum of ventricular fusion complexes of varying P-R and QRS intervals. Furthermore the appearance of this phenomenon including the time constants of the P-R and QRS intervals as well as the dependency of the anomalous QRS upon the sinoatrial node pacemaker is definitely related to the intensity of sympathetic efferent discharge and is associated most frequently with quite modest intensities of stimulation.

In all likelihood a dominant factor in the genesis of these arrhythmias is the concentration of norepinephrine at neuroeffector sites within the myocardium. Hoffman and Cranefield[7,8] have demonstrated the pronounced influence of norepinephrine on the rate of depolarization of cells of the Purkinje network in relation to cardiac rate and rhythm. In addition Han and Moe[9] have shown the differential responsiveness of closely adjacent areas of the ventricular myocardium to sympathetic stimulation. Thus, we may assume that differences in rates of diastolic depolarization in automatic cells after sympathetic stimulation could in all probability produce shifts in pacemaker activity leading to ectopic ventricular contractions.

Studies by Beattie, Brown and Long[10] and Magoun[11] among others, have shown that the hypothalamus sends efferent projections to the tegmentum, central gray substance and reticular formation of the midbrain and that fibers from these areas course chiefly through the lateral reticular formation of the medulla to terminate on preganglionic sympathetic neurons in the anterolateral funiculus of the spinal cord. The spectrum of arrhythmias described above was elicited from stimulation of neural loci in structures described by these writers as forming the descending connections. (Unpublished stud

ies from our laboratories have shown that cardiac arrhythmias can also be evoked during stimulation of the anterolateral funiculus in the distal end of the severed spinal cord of the cat.

More recently Nauta[12] has drawn attention to the multitude of reciprocal pathways between forebrain structures and the hypothalamus and midbrain. This vast network of interconnections and relays is not well understood and as Nauta points out little information is available as to the manner by which this complex limbic forebrain-midbrain circuit receives and transmits information to lower levels of the nervous system. This work underscores the gaps in our knowledge concerning autonomic function.

Summary

In order to assess the influences of the diencephalon and mesencephalon on the control of heart rhythm 24 adult beagle dogs were lightly anesthetized with Surital sodium and stimulating electrodes were guided stereotaxically into regions of the diencephalon and mesencephalon previously shown to elicit sympathetic responses. Symmetrical biphasic pulses of 1 to 2 Ma were delivered to these loci while the ECG was recorded from Standard Lead II. Electrical stimulation elicited a spectrum of ectopic ventricular rhythms. Observed in sequence were ventricular tachycardia both unifocal and multifocal ventricular premature contractions in bigeminal pattern and fusion contractions followed by a return to sinus rhythm. Although the entire spectrum was not evoked in all experiments the sequence of these abnormal rhythms was consistently the same. When an initial stimulus failed to elicit a response an increase in intensity usually evoked the entire spectrum. Bilateral vagotomy had no effect on the response however it was completely abolished by beta adrenergic blockade with propranolol (1 mg per kilogram). These data demonstrate that the type of arrhythmia observed is directly related to the intensity of sympathetic discharge and that all abnormal ventricular complexes observed in the clinic can be elicited.

We wish to express our gratitude to Mr. F. T. Grove, Mr. M. D. Banks and Mr. J. H. F. Pervall for technical assistance.

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Fundamentals of clinical cardiology

Clinical assessment of the function of the mitral valve in atrioventricular defects related to the anatomy

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In atrioventricular defects, the mitral valve is usually abnormal[1] and mitral regurgitation commonly results.[2] Since both anatomy and function of the mitral valve are variable, a critical examination of the incidence, signs, and severity of mitral regurgitation in patients with atrioventricular defects seemed to be worth while. In the present study clinical evidence of the function of the mitral valve has been related to the anatomy of the valve which was found at operation or necropsy.

Terminology

The term "atrioventricular defect"[3] has been used to describe the whole group of lesions which includes the ostium primum type of atrial septal defect, complete common atrioventricular canal and true single atrium. "Atrioventricular defect" is considered to be preferable to other terms used for the group such as "endocardial cushion defect"[4] and "common atrioventricular canal,"[5] because it indicates both the site of the defect and the fact that its clinical presentation has features in common with atrial and ventricular septal defects. Embryologically the term is correct. Van Mierop and his colleagues[6] showed that the septal defect in patients with atrioventricular defects lies in a special part of the septum which arises directly from endocardial cushion tissue, and which should be called the atrioventricular septum. Cases with ventricular septal defect, an abnormality of the atrioventricular valves and an intact atrial septum[7] are excluded by definition.

The present classification has three subdivisions of atrioventricular defects. The first is the *ostium primum* type of defect, in which the upper border of the ventricular septum beneath the atrioventricular valves, is functionally normal although it may be anatomically depressed; this defect is usually associated with abnormality of either the mitral or the tricuspid valve or of both. The next form of atrioventricular defect is the *common atrioventricular canal* composed of a functioning ventricular septal defect beneath the cleft atrioventricular valves, with an overlying ostium primum atrial septal defect. Patients with the intermediate form of atrioventricular defect, consisting of an ostium primum with cleft mitral and tricuspid valves and slight depression of the upper border of the ventricular septum are included in the group with ostium primum defect and intact ventricular septum (Table I) since clinically patients with the one

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Table 1 Type of atrioventricular defect method of confirmation of the anatomic diagnosis

Type of defect	*Number of cases*	*Number confirmed by operation*	*Number confirmed by postmortem*
Ostium primum	110	91	19 (9)†
Common A V canal	22	4	18 (6)
Single atrium	4	1	3 (2)
Total	136	96	40 (17)

*This includes 21 patients in whom the cleft of the anterior cusp of the mitral valve was continuous with a cleft of the septal leaflet of the tricuspid valve and beneath these leaflets the upper border of the ventricular septum was depressed (see text). Anatomic proof was obtained by operation in 12 patients and necropsy in the other 9 patients.
†Figures in parentheses are numbers of patients who died naturally.

lesion are usually indistinguishable from those with the other.[8] The third subdivision includes the *single atrium*. Patients with this rare lesion share most of the clinical and anatomic features of those with the other forms of atrioventricular defects, but their condition is classified as a separate entity. This diagnosis is only accepted when there is no remnant of the atrial septum and in these circumstances either the mitral or tricuspid valve is cleft or both are.

Material and methods

One hundred and thirty-six patients with atrioventricular defects in whom the anatomic diagnosis had been proved by inspection at the time of open heart surgery or necropsy or both were studied. They ranged in age from 2 weeks to 56 years, and the majority were under 20 years of age. The type of atrioventricular defect and the method of confirmation of the diagnosis are shown in Table I; the patients who died without undergoing surgery and those in whom necropsy was performed after unsuccessful surgery have been indicated. Important additional lesions were present in 14 patients: coarctation of the aorta occurred in 4 patients with ostium primum defect and stenosis of the pulmonary valve was present in 6 patients with ostium primum defect and in 4 with common atrioventricular canal.

The clinical severity of mitral regurgitation was assessed from the physical signs. The presence of electrocardiographic left ventricular hypertrophy[9] and the presence of left atrial enlargement on the chest radiogram were correlated with the clinical assessment of mitral regurgitation. A pansystolic murmur at the apex or the left sternal edge or both, which was heard either at rest or after exercise, was accepted as evidence of mitral regurgitation. When no pansystolic murmur was heard either at rest or after exercise, auscultation was repeated after 0.250 to 0.375 mg. of intravenous phenylephrine. The finding of an early or late systolic murmur at the apex was taken as evidence of trivial mitral regurgitation. Pansystolic murmurs were considered to be due to mitral regurgitation since in 85 per cent of the patients in sinus rhythm with signs of atrioventricular valve regurgitation the jet of regurgitation was clearly seen at operation to originate from the mitral valve. In the remainder of the patients either there were no operative observations or both mitral and tricuspid valves were seen to be regurgitant. However, in only one patient, whose tricuspid septal cusp was represented by a lump of fibrous tissue, was it more likely that the pansystolic murmur arose from tricuspid regurgitation than from mitral regurgitation.

The severity of mitral regurgitation was arbitrarily classified from the clinical findings into four grades. *Absent:* No early, late, or pansystolic murmur at the apex or left sternal edge at rest, or after effort, or intravenous phenylephrine, or both. *Trivial:* Inconstant pansystolic murmur or an early or late apical systolic murmur which became pansystolic after phenylephrine or after effort (Fig. 1). *Moderate:* Constant pansystolic murmur with or without mitral diastolic murmur. *Severe:* Constant pansystolic murmur often accompanied by a thrill, a mitral diastolic murmur, a third sound, with or without left ventricular hypertrophy.

In patients with common atrioventricular canal, the functioning ventricular septal defect theoretically could be the

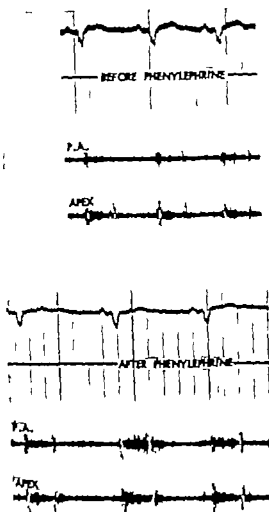


Fig. 1. External phonocardiogram from a patient with an early systolic murmur at the apex. Before phenylephrine, the high-frequency recording at the apex demonstrates the early systolic murmur beginning with the first sound and terminating in mid-systole. After intravenous phenylephrine the heart slows and the murmur at the apex becomes pansystolic with early systolic accentuation. Both tracings have the same standardization.

source of the signs which resulted from mitral regurgitation in other forms of atrioventricular defect. Since intracardiac phonocardiography has demonstrated that the pansystolic murmurs which are audible in some patients with common atrioventricular canal arise usually in the region of the mitral valve rather than in the right ventricle they have been attributed to mitral regurgitation.[1] However in view of the obvious difficulties of clinical assessment of the degree of mitral regurgitation in patients with common atrioventricular canal no distinction has been made between moderate and severe regurgitation. Cardiac catheterization was performed in all except 5 patients. Note was taken of a pressure gradient between the atria, and a large V wave in the left atrial pressure pulse.

The anatomy of the mitral valve was established by inspection at open heart operation or necropsy. Attention was given to the extent of the cleft in the anterior cusp of the mitral valve the presence of aberrant chordae[11] and abnormal insertion of chordae tendineae into the papillary muscles, and apparent deficiency of mitral valve tissue. The depth of the cleft was considered to be "complete" when it extended to the valve ring and "partial" when it was less extensive. These findings were specifically correlated with the degree of clinical mitral regurgitation. Other anomalies of the valve such as double mitral orifice, were recorded

Results

Clinical evidence of mitral regurgitation. The degree of mitral regurgitation found in patients with each form of atrioventricular defect is shown in Table IIA the frequency expressed as a percentage, has been separately indicated in Table IIB. In the patients with ostium primum defect, an analysis of physical signs arising from the abnormal mitral valve has been made (Table III). An opening snap occurring 0.10 to 0.12 second after closure of the aortic valve (A_2) has been shown to originate from the mitral valve in most patients with atrioventricular defects,[19] but its presence appeared to be unrelated to the severity of mitral regurgitation. Twelve of the patients who were considered to have trivial mitral regurgitation had apical early or late systolic murmurs which became pansystolic after effort or intravenous phenylephrine (Fig. 1). The remainder of the patients in this group had a pansystolic murmur which was either soft or evanescent, according to the patients physiologic state. In 2 patients the pansystolic murmur was only audible during pregnancy Nine of the 10 patients

with additional pulmonary stenosis were considered to have no clinical evidence of mitral regurgitation. Twenty-two patients with ostium primum defect had clinically moderate mitral regurgitation and in an additional 37 it was considered to be severe. The 4 patients with coarctation of the aorta had signs of severe mitral regurgitation.

Seven patients with common atrioventricular canal had no clinical evidence of mitral regurgitation; 3 of these had associated pulmonary stenosis. One patient was assessed as having trivial mitral regurgitation because of an early systolic murmur which became pansystolic after effort. The remainder of the patients had loud mitral murmurs and were classified as having important (moderate or severe) mitral regurgitation.

One of the 4 patients with single atrium had no clinical evidence of mitral regurgitation and in the other 3 patients, clinical assessment suggested that mitral regurgitation was moderate or severe. The clinical features were the same as those in the patients with ostium primum defect, except that there was no evidence of left atrial enlargement on the chest radiogram.

Anatomy of the mitral valve. In the patients with ostium primum defect the anterior cusp of the mitral valve was completely cleft in 77 patients (70 per cent), was partially cleft in 32 patients (29 per cent) (Fig. 2), and was accepted as normal in 1 patient, but this was not confirmed by necropsy. At operation 5 patients were considered by the surgeon to have a normal mitral valve, but 4 of them were subsequently shown to have a cleft anterior

Table IIA. Degree of mitral regurgitation in patients with atrioventricular defect

Type of defect	Number of cases	Degree of mitral regurgitation: None	Trivial	Moderate	Severe
Ostium primum	110*	22	29	22	37
Common A-V canal	22	7	1	14 (moderate and severe)	
Single atrium	4	1	—	1	2

*Includes 21 patients with defective ventricular septum and cleft tricuspid valve. Mitral regurgitation was absent in 2, trivial in 5, moderate in 6, and severe in 8 of them.

Table IIB. Frequency and severity of mitral regurgitation with different types of atrioventricular defect

Mitral regurgitation	Ostium primum defect (%)	A-V canal (%)	Single atrium (%)
None	20	32	25
Trivial	26	4	0
Moderate	20	64 (moderate and severe)	25
Severe	34		50

Table III. Clinical features of 110 patients with ostium primum defect related to the degree of mitral regurgitation present

Clinical features	Severe and moderate mitral regurgitation (number)	Per cent	Trivial mitral regurgitation or none (number)	Per cent
Thrill at left sternal edge or apex	27	46	1	2
Third sound at apex	21	36	3	5
Opening snap	17	29	7	12
Loud diastolic murmur	16	27	4	7
Left ventricular hypertrophy on ECG	19	32	3	5
Left atrium visible on chest radiogram	35	59	13	22



Fig 2 Heart from a patient with an ostium primum defect, viewed from the left. The lower arrow indicates a partial cleft in the anterior cusp of the mitral valve, with short aberrant chordae at the apex of the cleft. Above is a typical ostium primum atrial septal defect, and the upper arrow demonstrates a separate ostium secundum defect. This patient, 28 years old, had no clinical evidence of mitral regurgitation, and at open-heart operation was thought to have a normal mitral valve

cusp at reoperation or necropsy (Fig 2) Five of the 6 patients with associated pulmonary stenosis had a completely cleft mitral valve and the sixth patient had a partial cleft. The posterior cusp of the mitral valve was probably normal although it is frequently small in the patients with ostium primum defect and single atrium

The incidence and significance of aberrant chordae in the living patients cannot be analyzed Inspection of the mitral valve at operation probably yielded too low a figure (39 per cent) in contrast to the higher incidence at necropsy (74 per cent) at which time the under surface of the mitral valve was properly examined Abnormality of the insertion of the chordae tendineae into papillary muscles (Figs. 3 and 4) was never commented upon at operation but this was found at necropsy in 8 patients with ostium primum defect.

Patients with common atrioventricular canal had by definition complete cleft of the anterior cusp of the mitral valve which was continuous with the cleft in the septal cusp of the tricuspid valve. Aberrant chordae occurred commonly and were found in 13 patients examined at necropsy Eight patients had an abnormal insertion of the chordae tendineae or aberrant papillary muscles, or both. Both anterior and posterior cusps were frequently misshapen and poorly differentiated (Fig 5)

Three of the patients with single atrium had a complete cleft in the mitral valve, and the fourth patient had a partial cleft. In 1 patient with single atrium the complete cleft was continuous with a cleft in the tricuspid valve. Aberrant chordae were found in one patient and none of them had aberrant papillary muscles or anomalous insertion of the chordae tendineae.

Double mitral orifice was found in 1 patient with ostium primum defect, in 1 of the patients with common atrioventricular canal (Fig 6)

Relationship of the severity of mitral regurgitation to the anatomy of the mitral valve The assessed degree of clinical mitral regurgitation has been related to the depth of the cleft found in the mitral valve in the patients with ostium primum defect (Table IV) Four of the 22 patients with no clinical evidence of mitral regurgitation had a completely cleft anterior cusp of the mitral valve, and in 17 there was a partial cleft Of the group with trivial mitral regurgitation 22 had a complete cleft, and 7 had a partial cleft. In all of the patients with ostium primum defect who were considered to have trivial or absent mitral regurgitation the two halves of the anterior cusp appeared at operation to approximate easily The cusps were well formed and able to billow up in systole the tendinous insertions of the cusps were long and no patient in this group was found to have an abnormal or aberrant papillary muscle. Short aberrant chordae were found in 19 patients and were usually confined to the apex of the cleft (Fig 2)

The anterior cusp of the mitral valve was completely cleft in 17 of the 22 patients with ostium primum defect whose mitral regurgitation was clinically assessed as moderate the other 5 patients had a partial cleft In 15 patients the



Fig. 3. Necropsy specimen from a patient with small ostium primum defect and severe mitral regurgitation viewed from the left. There is a partial cleft in the mitral valve (*white arrow*). The anterior papillary muscle and chordae are grossly abnormal (*lower black arrow*). The upper black arrow indicates the small ostium primum defect. The cm mark indicates the severity of left ventricular hypertrophy.



Fig. 4. Heart from a patient with severe mitral regurgitation and ostium primum defect, showing the under surface of the mitral valve. The upper arrow shows the cleft in the anterior cusp which has been sutured. The lower arrow indicates the abnormal papillary muscle inserted directly into the anterior cusp of the mitral valve; no proper chordae tendineae have formed this attachment.

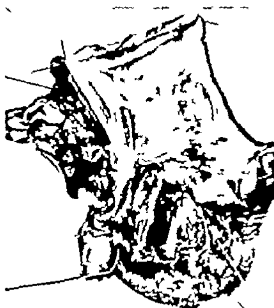


Fig. 5. Heart viewed from the left from a patient with common atrioventricular canal who had clinically severe mitral regurgitation. The two halves of the anterior cusp of the mitral valve are thickened and deficient; the tendinous insertions are short, thick, and abnormally placed.

Table IV Anatomy of the mitral valve in patients with ostium primum defect related to degree of mitral regurgitation

Mitral regurgitation	Number	*Cleft in anterior cusp*		Mitral valve normal
		Complete	Partial	
Severe	37*	34	3	0
Moderate	22	17	5	0
Trivial	29	22	7	0
None	22	4	17	1
Total	110	77	32	1

*One patient had double mitral valve.

regurgitant jet was seen at operation to be localized and narrow and most commonly situated at the apex of the cleft in the region of the ventricular septum Failure of the cusps to meet in a small area was related either to irregularity and thickening of the cusps or to aberrant chordae holding down the edge. In 7 patients the jet of incompetence was wider and more severe than had been suspected clinically Aberrant short chordae were noted in 9 of the 22 patients with clinical moderate mitral regurgitation 5 of them had a narrow localized jet, and 4 were in the group of 7 who had a diffuse wide jet of mitral regurgitation. One patient who was considered to have moderate mitral regurgitation had a short abnormal tendinous insertion of the anterior cusp and clinical assessment had underestimated the disturbance of the mitral valve.

In the other 34 patients with ostium primum defect whose mitral regurgitation was clinically assessed as severe the cleft was complete in all but 3 patients. One patient with complete cleft had a double mitral orifice, and severe mitral regurgitation was due to partial destruction of both halves of the anterior cusp by bacterial endocarditis. At operation 11 patients who had been clinically assessed as having severe mitral regurgitation were found to have only a narrow localized jet, as was observed frequently in the group considered to have moderate mitral regurgitation Thus clinical assessment in these patients overestimated the severity of the mitral regurgitation In the other 23 patients, clinical appraisal correctly assessed the severely disturbed anatomy and function of the mitral valve. In all 23 patients with severe mitral regurgitation there was an apparent deficiency of cusp tissue which prevented apposition in systole of the parts of the anterior cusp with either each other or with the posterior cusp or both. Observation at operation showed that the cusps could not balloon up and so remained slanting down into the cavity of the left ventricle. This disturbance of function resulted from a number of different factors namely unusually high attachment of the superior portion of the anterior cusp, deficiency of cusp tissue short abnormal tendinous insertion into papillary muscles, and abnormal papillary muscles. In 7 of 9 patients with severe mitral regurgitation who came to necropsy the tendinous insertion was abnormal (Fig 3) and in 4 the abnormal papillary muscle inserted directly into the cusp (Fig 6) Aberrant short chordae holding down the edges of the cusp were noted in 6 of the patients examined at necropsy and in another 7 who were studied only at operation Although the incidence of aberrant chordae was not higher in the patients with severe mitral regurgitation when present, they extended along a greater length of the edges of the cusp than in the patients with a lesser degree of mitral regurgitation

In 8 patients with common atrioventricular canal and clinically assessed absent or trivial mitral regurgitation the cusps of the mitral valve were well formed and the chordae tendineae were long Five of these patients had aberrant chordae, and 1 had a double mitral orifice with multiple aberrant chordae. Among the other 16 patients with common atrioventricular canal and clinical evidence of established mitral regurgitation mitral regurgitation was observed at operation or obvious cusp deficiency at necropsy or both Four of the 16 patients had a localized regurgitant jet which probably represented moderate mitral regurgitation and was due to a combination of thickening and shortening of cusp tissue ...



Fig 4 Necropsy specimen of complete common atrioventricular canal showing double mitral valve viewed from above The white arrow is in the superior vena cava and points toward the anterior surface of the heart. The atrial septum has been cut away and on the left the mitral valve has two orifices The anterior orifice is larger On the right is the tricuspid valve

tethering by chordae at the point of incompetence In the other 12 patients the parts of the mitral anterior cusp were poorly developed (Fig 5) and had no opportunity of meeting in systole. In addition to the real deficiency of cusp material there was tethering of the cusps by aberrant chordae in all of the patients and by abnormal tendinous insertion into papillary muscles in 6 patients. In 3 patients the superior portion of the anterior mitral cusp was attached by chordae arising from a papillary muscle on the right side of the ventricular septum.

The anatomy of the mitral valve in patients with single atrium was the same as that in patients with ostium primum defect. Severe mitral regurgitation was present in 1 patient who had a partial cleft. Clinical moderate mitral regurgitation was noted in 2 patients with a complete cleft, and in the other patient with complete cleft there was no evidence of regurgitation None had abnormal papillary muscles or short tendinous insertion and in 2 short aberrant chordae were found

Discussion

Clinical assessment of the severity of mitral regurgitation in patients with any form of atrial septal defect is difficult and the presence and the importance of associated tricuspid regurgitation is harder to evaluate Experience has shown that severe tricuspid regurgitation is rare in patients with atrioventricular defects who have sinus rhythm and that it is usually correct to assume that pansystolic murmurs originate from the mitral valve in these patients. In patients with atrioventricular defects and an established arrhythmia such as atrial fibrillation nodal bradycardia or complete heart block tricuspid regurgitation may develop and be severe[4] as a result of dilatation of the tricuspid ring Under these circumstances clinical assessment of mitral regurgitation was made from the signs present when the patients were in sinus rhythm The clinical signs of mitral regurgitation in patients with atrioventricular defects may at first suggest tricuspid regurgitation since the pansystolic murmur is often maximal at the left sternal edge and increases with inspiration in many patients. In most of the patients with these physical signs, there has been neither anatomic nor physiologic evidence to support the diagnosis of tricuspid regurgitation and the mitral valve has been found to be incompetent at operation The intracardiac phonocardiogram has provided further evidence about the mitral origin of signs in atrioventricular valve abnormality The frequently noted pansystolic murmur and thrill at the left sternal edge arise from the mitral valve and are related to the position of the jet of mitral regurgitation in atrioventricular defects. This unusual site for mitral thrill and murmur results from the regurgitant jet occurring through the anterior cusp and often being directed anteriorly through the ostium primum defect toward the lateral wall of the right atrium This may also give rise to a palpa

ble thrill beneath the right nipple, as was noted in 8 patients.

In the patients with ostium primum defect and functionally intact ventricular septum electrocardiographic left ventricular hypertrophy occurred more frequently in patients with severe mitral regurgitation. It was not present in every patient with important mitral regurgitation since its development was in part related to the size of the atrial septal defect. In the presence of an atrial septal defect occupying one third or more of the atrial septum the effects of mitral regurgitation are transmitted mainly to the right side of the heart, so that left ventricular hypertrophy may not develop even if severe mitral regurgitation is present.

When mitral regurgitation was clinically assessed as being trivial or absent, it was found to be an accurate indication of the slight functional disturbance noted in the mitral valve at operation even though the mitral valve was anatomically abnormal in all except one patient. A partial cleft in the anterior cusp was found more frequently in this group of patients than in those in whom the mitral regurgitation was assessed as being moderate or severe. Short aberrant chordae were noted in 19 of the 49 patients with absent or trivial regurgitation and their presence, usually at the apex of the cleft (Fig 2) did not appear to interfere much with apposition of the cusps. None of the patients with trivial or absent mitral regurgitation was found to have abnormal papillary muscles or short, malformed tendinous insertions. Since necropsy was performed in only 7 of these patients it is possible that, in spite of the trivial mitral regurgitation aberrant or abnormal papillary muscles may not have been detected

In the patients with ostium primum defect whose clinical signs suggested moderate or severe mitral regurgitation it was not possible to be certain of the extent of the functional and anatomic disturbance of the mitral valve on the basis of the bedside examination alone. Seven patients who were assessed as having moderate mitral regurgitation, and 23 of the 34 patients with signs of severe mitral regurgitation had wide jets of mitral regurgitation which resulted from the inability of the anterior mitral cusps to rise up into the left atrium and meet in systole. This form of mitral regurgitation was due to a number of factors, such as cusp deficiency high attachment of the superior portion of the anterior cusp aberrant chordae at the edge, and abnormal tendinous insertion into papillary muscles (Figs. 3 and 4) The presence of abnormal tendinous insertion and deformed or aberrant papillary muscles caused the most severe and irreparable mitral regurgitation and these were found in one third of the patients whose mitral regurgitation was confirmed to be severe at operation Suture of the cleft in such patients resulted in worsening of the mitral regurgitation or mitral stenosis which usually caused fatal pulmonary edema after closure of the atrial septum It is possible that such patients require operation through the left atrium with possible replacement of the mitral valve. Recognition of mitral valve disturbance which is inoperable by the conventional surgical techniques used for closing atrioventricular defects is vital Clinical signs of florid mitral valve disease should suggest the possibility but left ventricular angiography is necessary[11] in order to define the anatomy of the mitral valve. Although aberrant chordae at the edge of the cusps can contribute to mitral regurgitation they do not appear to be the major cause of severe mitral regurgitation unless they extend along most of the edge of the cleft Their presence has been confirmed in patients with a clinically competent mitral valve. Although a partial cleft is more common in patients with trivial or absent mitral regurgitation the degree of mitral regurgitation cannot be related to the depth of the cleft, since patients with a complete cleft had clinically competent mitral valves, and a few with a partial cleft had gross mitral regurgitation at operation.

Mitral regurgitation was not recognized clinically in 9 of the 10 patients with additional pulmonary stenosis. However at operation 4 were seen to have a regurgitant jet arising from the mitral valve, which was severe in one and caused pulmonary edema when the defect was closed It is likely that the long loud ejection systolic murmur arising from the pul-

monary stenosis dominated auscultation and made clinical recognition of an additional pansystolic murmur difficult. Thus in patients with pulmonary stenosis and an atypical electrocardiogram suggesting atrioventricular defect,[13] investigations such as left ventricular angiography and intracardiac phonocardiography should be undertaken in order to find evidence of mitral regurgitation and an underlying atrioventricular defect.

All 4 patients with coarctation of the aorta in this series had severe clinical and anatomic mitral regurgitation. 3 had short tendinous insertion and 1 had abnormal papillary muscles. Although this is a small number of patients on which to base conclusions, it suggests that the mitral valve in patients with atrioventricular defects and coarctation may not be reparable from the right atrium.

In spite of the cleft in the anterior cusp the mitral valve was found to be clinically competent under different physiologic conditions in 20 per cent of patients with ostium primum defect, and others were shown to have mitral regurgitation only after excitement, effort, or pregnancy. In such patients repair of the atrioventricular defect carried less risk of postoperative mitral valve dysfunction. In patients with single atrium, the incidence of mitral regurgitation and anatomic disturbance in the mitral valve was the same as in the patients with ostium primum defect. It is of interest that 8 patients with the severe common atrioventricular canal were found to have either trivial mitral regurgitation or none. Three of the patients had pulmonary stenosis, so that it is possible that the mitral regurgitation was missed in these. Three of the remainder of the patients with no mitral regurgitation had the Eisenmenger reaction, and it is likely that in the absence of a left-to-right shunt and important cardiac enlargement, the abnormal but well-developed atrioventricular cusps could approximate in systole.

It is difficult for surgeons to assess the importance of aberrant chordae, abnormal cusp deficiency, and tendinous insertion with aberrant papillary muscles from the limited view of the mitral valve through the ostium primum defect. This accounts for many of the difficulties and disasters in attempts to repair the severely disordered mitral valves in some patients with atrioventricular defects and also explains the error of surgical observation on the normality of the mitral valve. A normal mitral valve in association with an atrioventricular defect is exceptional and requires necropsy confirmation before it can be accepted.

Summary

The clinical assessment of mitral valve function has been related to the anatomy and function of the mitral valve found at operation or necropsy in 136 patients with atrioventricular defects. Clinical assessment of absent or trivial mitral regurgitation indicated accurately the slight functional disturbance found in the mitral valve.

Sixty per cent of patients with florid clinical signs of mitral regurgitation had severe physiologic and anatomic disturbance of the mitral valve which resulted from a number of factors and was not related to the depth of the cleft. The importance of short tendinous insertion and abnormal papillary muscles in causing severe mitral regurgitation is emphasized.

Mitral regurgitation may be unrecognized in the patients with additional pulmonary stenosis and is likely to be severe when coarctation is present. The mitral valve was found to be clinically competent in 20 per cent of the patients with ostium primum defect and single atrium, and in 10 to 15 per cent of those with common atrioventricular canal.

I am grateful to the physicians and surgeons of Guy's Hospital, the Middlesex Hospital, National Heart Hospital, and Sick Children's Hospital, Great Ormond Street, who have permitted me to study their patients. I wish to thank Dr. Lawson McDonald and Dr. Leon Resnekov for advice in writing this paper, Dr. Reginald Hudson for the photographs of the specimens shown in Figs. 2, 3, 5, and 6, and Dr. Walter Somerville for Fig. 4.

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Antianginal drugs Part IV The long-acting nitrates

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Since it was reasoned that nitroglycerin-like compounds with a long duration of action might be helpful in the prophylaxis of angina pectoris a variety of long-acting nitrates have been made available for clinical use. Four widely used compounds will be described briefly; in general the comments made in the first three articles in this series are equally applicable to these compounds.

1 *Pentaerythritol tetranitrate* or PETN is the most popular prototype the best known commercial preparation is Peritrate. It is available for oral use in 10-mg and 20-mg tablets and in sustained release preparations containing 80 mg of the compound. There is a sublingual preparation consisting of 10 mg of PETN with 0.3 mg of nitroglycerin. It has also been compounded with hydrochlorothiazide (Perithiazide) and a variety of sedatives hypnotics and tranquilizers such as phenobarbital secobarbital etc. meprobamate (Equanitrate Miltrate) and hydroxyzine (Cartrax). All told there are over 30 different commercial preparations which contain this drug alone or in combination. PETN is claimed to appear in the blood stream in about 30 to 60 minutes and disappears in about 4 to 5 hours. The sustained-release preparation is said to persist for about 12 hours.

The usual oral recommended dose is 10 to 20 mg four times daily or one sustained release tablet on arising and again 12 hours later.

2 *Erythrityl tetranitrate* (Cardilate) is available in 5-mg 10-mg and 15-mg tablets for oral or sublingual use; the 10-mg dose has been combined with 15 mg of phenobarbital. The usual starting dose is 5 to 10 mg three times daily and this may be increased to up to 30 mg three times daily. For greater rapidity of effect, the sublingual route may be used. The rate of dissolution which was quite slow has been improved. The drug can cause a drop in systolic blood pressure. There is no sustained release preparation available.

3 *Isosorbide dinitrate* (Isordil) is available in 10-mg and 5 mg tablets for oral and sublingual use respectively. The oral dose has been combined with 15 mg of phenobarbital and a 40-mg sustained-release tablet (Isordil Tembids) is also marketed.

The effect is said to begin in 15 to 30 minutes and lasts about 4 hours after oral use. The sublingual preparation claimed to be stable for years has been said to compare favorably in speed of action with nitroglycerin and the effect lasts longer. The sustained-release tablet is claimed to provide a drug level within 30 minutes and to act for about 12 hours. The recommendeded doses are (a) oral tablet, with or without phenobarbital ½ to 3 tablets four times daily (b) sublingually 1 or 2 tablets every 4 hours, with additional tablets used in situations likely to induce an anginal attack (c) sustained release preparation 1 tablet twice daily at 12 hour intervals.

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4. *Trolnitrate phosphate* (Metamine Nitretamin) is available in 2 mg tablets with or without 15 mg of butabarbital or 10-mg sustained-release tablets alone or with 0.1 mg of reserpine or with 50 mg of butabarbital. The oral dose is 1 to 2 tablets four times daily One of the butabarbital-containing tablets can be given before meals and 1 or 2 at bedtime. The sustained-release preparation of the nitrate is administered at intervals of from 6 to 12 hours for a total of no more than 4 per day

There is no significant information to point to any basic difference in the pharmacology of these compounds. Thus the mechanism of action precautions, and side effects are those common to organic nitrates. Like nitroglycerin, they produce peripheral vasodilatation and headache. The incidence of headaches is greater with some than with others, but this appears to be related to the dose rather than to differences in pharmacodynamics. We have been unable to demonstrate that maximally tolerated doses, using headache as a guide, improve the efficacy of these compounds. Unlike nitroglycerin these drugs are intended to be given more or less continuously When any of these agents is given continuously tolerance will develop rapidly so as to block whatever vascular effects it has.

As in the case of nitroglycerin there are various studies which show enlargement of the large coronary arteries in man and various experimental animals after the administration of these drugs, and studies which show 'beneficial effects on the electrocardiogram.

Therapeutic claims made for one of these agents that have not been made for nitroglycerin are that pentaerythritol tetranitrate improves the chances for survival of patients with acute myocardial infarction and their postinfarction long term survival In the published study 100 patients were involved The series was small other forms of therapy were not maintained constant and the death rate of the control group was remarkably high It is a beginning but no conclusions can be made A large, well-designed cooperative study will be necessary to resolve this question.

It is monotonous but nevertheless very important to reiterate that the efficacy of these antianginal agents must be gauged only by the results of carefully controlled studies designed to test their effect on angina pectoris. Whether the studies have concentrated on the effect of these drugs on spontaneous clinical angina or on experimentally induced postexercise angina the availability of satisfactorily controlled studies (cross-over double-blind with random assignment of drug and its indistinguishable placebo) is appallingly limited Even the more desirable laboratory studies on exercise-induced angina have diminished significance because they have not followed a double-blind design, and because the environmental temperature has been maintained at a chilly 45 to 55°F thereby complicating interpretation Furthermore classifying the patients according to responsiveness to the drugs and then determining efficacy on the responsive patients as has been done in these studies, is a highly questionable procedure

Considerably better work must be done to determine the efficacy of these agents. Pending collection of meaningful information I must conclude that the therapeutic value of these agents has not been proved satisfactorily and hence they cannot be recommended for the treatment of angina pectoris or for any of the stages of coronary artery disease Accordingly it is irrelevant to discuss further their pharmacology indications, contraindications, dosage, comparative efficacy or toxicology beyond what has already been said

It is regrettable that so much irrelevant work has been done with some of these agents before a concerted effort was made to prove whether they possess therapeutic usefulness In my opinion they have remained in active use because physicians need to prescribe something rather than nothing and most importantly because of the elusiveness of the anginal syndrome and its responsiveness to placebo

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Angiotensin infusion test in hypertension

It is often difficult to distinguish hypertension due to renovascular disease from essential hypertension. Although a renal lesion in a hypertensive patient can often be demonstrated either by pyelography or renal arteriography, surgical attack on a unilateral lesion is no guarantee of permanent lowering of the blood pressure. Some patients, however, do benefit from surgery, but selection of those likely to respond favorably constitutes a challenge. Divided renal function studies have been disappointing because of difficulties both in technique and in interpretation of results. Renal biopsy, unilateral or bilateral, has been advocated, but sampling errors make interpretation difficult.

Measurements of blood levels of renin or its derivative angiotensin have also been used to decide whether a kidney should be removed as radical treatment for hypertension; these are difficult techniques which cannot yet be applied in every hypertensive patient. Moreover, although the levels of these substances in the blood are often increased in patients with chronic renovascular hypertension, this is not always so. It has been suggested that measurement of these levels in renal venous blood is a better guide.

Kaplan and Silah have proposed an indirect method of measuring circulating angiotensin. They argued that patients whose hypertension is associated with an excess of circulating angiotensin should be relatively insensitive to a further infusion of angiotensin, whereas hypertensive patients in whom the renin-angiotensin system plays no part will indicate sensitivity by a large rise in blood pressure after infusion. The test consists of infusing angiotensin intravenously in a concentration of approximately 0.3 μg per milliliter until a rise in diastolic blood pressure of 20 mm. Hg is obtained and sustained for 10 minutes. If the amount of angiotensin which must be given to produce this response is greater than 6.5 mμg per kilogram of body weight per minute, the test is positive and the patient might be expected to have functionally significant renovascular hypertension. False-positive results may occur in patients who have malignant hypertension or a diminished plasma volume as a result of diuretic therapy, in which cases an increased amount of circulating angiotensin can be present. If the amount of angiotensin necessary to produce a rise in blood pressure of 20 mm. Hg falls below 6.5 mμg per kilogram of body weight per minute, the test is negative and functionally significant renovascular hypertension is alleged not to be present. The empirical figure of 6.5 mμg per kilogram per minute is based on Kaplan and Silah's experience of the test in over 180 subjects. Of these only 16 were consistently resistant to the infusion of angiotensin, and these all had a renal lesion and the pattern of renal ischemia on divided renal function studies. In 43 patients who had abnormal intravenous pyelograms and yet had normal divided function studies, the blood pressure rose on infusion of a small dose of angiotensin. Seventy-seven patients with essential hypertension were all found to be sensitive to infusion of angiotensin.

So far, there have been three reports of other series of angiotensin-infusion tests, but Kaplan and Silah's results have not been confirmed. In a detailed series Breckenridge performed the test on 59 occasions in 40 hypertensive patients. Although detailed and exhaustive investigations in 16 patients had failed to show renal lesions which might be the cause of the hypertension, 5 were resistant to infused angiotensin. There were 15 patients with unilateral renal disease. Nine of these responded to a small dose of angiotensin by a rise in blood pressure, whereas 6 were resistant to the infused substance. Of the 15 patients, 3 were subsequently subjected to operation, and a 6-month follow-up has shown that the results of the angiotensin infusion test have not helped in predicting those who will benefit from surgery. It was also shown that the results of the test are reproducible and that drug treatment of hypertension has little influence on the result. Wax has confirmed these conclusions. Of 46 patients who were considered to have essential hypertension, 21 were insensitive to infused angiotensin, and in another series of 61 patients, Morgan found 6 false-positive results and 3 false-negative ones.

The early promise of this test has not been fulfilled, which is hardly surprising because the renin-angiotensin system is perhaps not so directly concerned with the genesis of hypertension as was originally thought. The present angiotensin infusion test cannot solve the problem of surgical selection in renal hypertension, although the problem of variable sensitivity may be of continuing scientific interest.

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Phenacetin, aspirin, and kidney damage

In 1953 Spühler and Zollinger[1] described 44 cases of interstitial nephritis often accompanied by papillary necrosis in subjects who did not have diabetes or obstruction of the urinary tract. Fourteen of these subjects had been heavy consumers of analgesic mixtures containing phenacetin. Many reports followed from various parts of the world, particularly from Switzerland and Scandinavia, where the habitual consumption of phenacetin appears to be relatively common, confirming an association between prolonged heavy consumption of phenacetin and kidney damage; these are listed in a comprehensive account of toxic nephropathy and a long term follow-up study on 3 such patients has also been published recently. In this way a strong case has been made for the nephrotoxic properties of phenacetin, a drug already known to augment the formation of methemoglobin and, rarely, to induce a drug-dependent antiglobulin reaction causing hemolytic anemia.

A causative association between the heavy consumption of analgesics and kidney damage has come to be generally accepted on the basis of this convincing, although indirect, evidence, but the assumption by most earlier European writers that phenacetin is the responsible agent has been criticized on the grounds that drug mixtures are implicated rather than single therapeutic agents. A discerning pharmacologic review by Gilman[4] discusses various possible mechanisms of drug nephrotoxicity and makes the special point that aspirin may be the harmful drug rather than, or in addition to, phenacetin.

There are good reasons for considering this possibility. (1) Aspirin is a constituent of many phenacetin-containing analgesic tablets. (2) Renal failure has been known to follow acute overdosage of aspirin. (3) Salicylates are known to have a damaging effect on other epithelial surfaces, particularly in relation to the production of gastrointestinal

hemorrhage (which is fortunately nearly always of small magnitude). (4) Renal tubular cells appear in the urine after ingestion of salicylate.[8]

The presence of aspirin in many compound analgesic tablets naturally makes the situation a difficult one to analyze but aspirin has not always been included in the offending mixture. For example there are reports of renal damage after the use of Saridone a compound containing propylphenazone phenacetin and caffeine but no salicylate. Moreover plain aspirin is used extensively in maximum tolerated dosage for the long term treatment of such conditions as rheumatoid arthritis, but to date with the exception of a single individual in a large survey of patients with renal papillary necrosis[10] there have been no reports of renal papillary necrosis and interstitial nephritis attributable to aspirin alone despite a general current awareness of the problem. The corresponding argument that renal damage has not been reported after the prolonged consumption of plain phenacetin is of little significance because although phenacetin is available in simple form and appears as such in both the British and United States Pharmacopeias, it is unlike aspirin hardly ever prescribed or taken as such. Still, if nephropathy follows the use of aspirin plus phenacetin, but not that of aspirin alone then this is surely inferential evidence that in so far as these two drugs are concerned phenacetin is the harmful one.

With regard to the second point renal failure after the use of plain aspirin has been a matter of acute massive overdosage and not of its use in clinical practice.

As to the third and fourth points it certainly seems that salicylate has a widespread action upon epithelial surfaces. The exact mechanism of the gastrointestinal hemorrhage which is caused by salicylate remains uncertain but it is probably related to an increased rate of exfoliation of gastric cells.[11] The exfoliation of renal tubular cells follows an interesting sequence provided that the subject has taken no salicylate during the preceding few weeks a striking increase in the cell count in the urine rapidly occurs after administration of the drug reaching a maximum on the second or third day. The count later returns to normal or nearly normal levels even if treatment is continued. After the administration of aspirin ceases there is a refractory period during which repeated administration produces only a diminished cellular response. Therefore, it appears that aspirin causes a transient shedding of renal cells which have achieved a certain degree of maturity the refractory period representing the time necessary for young cells to achieve an age at which they become subject to the influence of salicylate. To assume from this phenomenon that salicylate in therapeutic dosage causes chronic renal damage is on present evidence unwarranted. A recent study[18] confirming the effect of salicylate on the kidney reported similar but very much smaller increases in renal tubular cell counts after paracetamol, caffeine and phenacetin as well.

It might be hoped that animal experiments would help to resolve the rather confused situation which has developed but this approach has so far been inconclusive. The administration of phenacetin to animals has usually failed to cause renal damage and conflicting results have been obtained when administration of the drug has been combined with hematogenous infection—a situation whose relevance to clinical problems is in any case questionable. Results of animal work are briefly reviewed by Dawborn Kincaid Smith and McLaren[12] who themselves found no significant difference in the kidneys between control animals and rats which had been given phenacetin aspirin or a combination of both drugs for 5 months. Nor was there any evidence from these experiments that the renal inflammatory lesions produced by intravenous injection of bacteria were more severe or frequent in the rats given analgesic drugs. In other recent studies however renal papillary necrosis has been reported in rats after salicylate[14]; phenacetin was found to produce medullary cellular changes cortical pigmentation and occasionally papillary necrosis in rats[13] and aspirin and phenacetin caused tubular and interstitial changes in rabbits (with occasional papillary necrosis in the case of phenacetin)[15]—but very large doses were used in the latter two studies.

Although there is therefore as yet no conclusive evidence that phenacetin itself is the sole cause of the renal lesions in question and other analgesics may play a greater or a lesser part, the evidence for chronic aspirin nephrotoxicity rests on no surer ground than that for phenacetin. And aspirin is a far more useful drug than phenacetin. Apart from its use as an occasional analgesic and its antipyretic and anti-inflammatory effect in rheumatic fever it is still the best drug for most patients with rheumatoid arthritis in whom, by relieving pain and permitting planned exercise it helps to prevent the development of deformity. No doubt the indiscriminate use of analgesic tablets should be discouraged but it would be a pity if the legitimate use of long-term salicylate therapy were jeopardized by the fear of hypothetical dangers.

At the present time increasing attention is being paid to the necessity of carefully registering the harmful effects of all drugs both by individual communications and by reports to various central authorities which are being established in many countries. In the case of analgesic nephrotoxicity wherein animal experimentation has so far given results of uncertain meaning and prospective epidemiological studies will clearly present many difficulties careful clinical and pathologic reports will probably remain our major source of information for some time. The absence of such reports with regard to aspirin alone will also be of considerable significance.

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Kinekard*

The concept that the plasma of circulating blood contains substances which influence the activity of the heart and blood vessels is of long standing, and in recent years, experimental data supporting this contention have been accumulated. This subject was reviewed in an editorial in this JOURNAL in 1965. That the mechanism which controls cardiac activity and the selective supply of blood to various regions of the body contains both nervous elements and fluid pathways carrying chemical messengers is becoming more firmly established with the increasing knowledge[1-4] of the roles of catecholamines, oxytocin, vasopressin, bradykinin, and angiotensin. However, this array of substances, which can be recovered from the blood with varying degrees of difficulty, is inadequate to account for all the data which imply the presence of circulating substances. It is of considerable interest, therefore, that a group of workers at the Baker Medical Research Institute in Melbourne, Australia, have isolated from the blood plasma of many species of animals[5] another substance which has a powerful action on both heart and blood vessels and shows no species specificity. They have for convenience called this substance *kinekard*.

Kinekard can be separated from heparinized blood plasma by gel filtration followed by ion-exchange chromatography on diethylaminoethyl-methacrylate gel[7] and has been recovered from man, monkey, dog, rabbit, rat, tortoise, lizard, fowl, guinea pig, and lamprey. On high-voltage electrophoresis it runs as a single ninhydrin-reacting band with an isoelectric point of pH 6.8. Its molecular weight has been estimated to be in the range of 5,000 to 8,000. Its biologic activity is completely destroyed by incubation at pH 7.0 with the carboxypeptidase subtilisin. Kinekard appears to be remarkably stable and can be recovered from whole blood or plasma which has been cold-stored for considerable periods. With present methods of extraction, approximately 60 μg can be recovered from 1 liter of human plasma.

The addition of kinekard to the perfusate of isolated perfused amphibian or mammalian hearts produces a marked positive inotropic response which is not blocked by the β-adrenergic antagonist pronethalol. On a weight-for-weight basis the inotropic action is ten times greater than that produced by norepinephrine. This inotropic response is associated with augmented oxidative metabolism in both the perfused heart and in heart muscle homogenates. There is also a decrease in the duration of the ventricular action potential which is produced by an increase in the rate of repolarization.

The action of kinekard when injected intravenously into an anesthetized rabbit has been studied and a dose of 0.025 to 0.05 μg per kilogram produces a marked pressor response which is not blocked by prior reserpinization or prior adminis-

*A portion of the studies described were carried out with grant-in-aid from the Life Insurance Medical Research Fund of Australia and New Zealand.

tration of pronethalol or bretylium tosylate. This pressor response is associated with an equally marked *immediate increase in cardiac output.* Neither response is modified by prior bilateral adrenalectomy or nephrectomy.

In dogs with the heart and lungs bypassed with a heart-lung machine and in various isolated hind limb preparations the direct action of kinekard on blood vessels can be demonstrated and it is completely abolished by *the addition to the circulation* of the α-adrenergic antagonist phenoxybenzamine in amounts of 15 mg. per kilogram. The pressor response is accompanied by a redistribution of blood flow in various regions, there being a decrease in the hind limb and renal vascular bed and an increase in coronary blood flow, this last occurring whether the heart is or is not *artificially paced* or performing useful work.

The direct action of kinekard on vascular muscle can be shown on isolated strips of rabbit aorta suspended under isometric conditions and is here blocked by the α-adrenergic antagonists phenoxybenzamine and dihydroergotamine. The similarity *of this action and blockade to that of epinephrine* suggests that the action of kinekard is here related to the α-adrenergic mechanism.

Kinekard also acts on nonvascular muscle producing relaxation and cessation of spontaneous contractions of an isolated segment of rabbit ileum and inhibiting spontaneous contractions and acetylcholine-*induced contractions in an isolated uterine* segment (*unpublished data*).

By using a *biologic* assay based on inotropic activity and relating this to the response to norepinephrine, it has been possible to determine the level of circulating kinekard in the venous blood of man in terms of an arbitrary unit equivalent to *1 μg. of norepinephrine per liter. In a small series* of normal individuals the plasma level was between *21 and 35* units. *In a* series of patients with a variety of disease states a group with levels below and a group with levels above the normal range were found, but no correlation between plasma level and disease state, age, sex, or arterial blood pressure was apparent. In this paper, however, the authors commented upon the change produced in the plasma *level of kinekard by surgical interference* with the hypothalamic pituitary region. Possibly this should be associated with the observation that plasma kinekard activity is very low in the hibernating toad but can be restored to normal levels by the parenteral injection of anterior pituitary extract 48 hours before measurement[10] to suggest that in some way *this region of the nervous system is* involved in the control of circulating kinekard.

It will be noted from this summary of data on kinekard that there are many similarities to and differences from various other circulating plasma substances which act on the vascular system. The molecular weight of kinekard differentiates it from *the previously mentioned polypeptides* and catecholamines. It seems to be likely that its pressor *activity is mediated through α-adrenergic receptors* but not by the release of locally stored catecholamines, for this action is not blocked by prior administration of bretylium tosylate nor does kinekard release them from the adrenal medulla like angiotensin and bradykinin.[11] Its inotropic action in circumstances in which the catecholamines are *blocked clearly distinguishes it from them.* The failure of nephrectomy to influence the action of kinekard suggests that the renin angiotensin system is not involved, and the absence of a biphasic effect on cardiac output also differentiates it from angiotensin.[9] Its inotropic activity in the isolated heart and its pressor activity set it apart from bradykinin. *Its ability to increase coronary blood flow is in* contrast to vasopressin and oxytocin,[2,4] as is its action on ileum and uterus in contrast to angiotensin, oxytocin, bradykinin, and vasopressin.[2]

From the published data it seems that kinekard is a *previously unknown* highly potent stable plasma constituent that may be a component of the mechanism which regulates the cardiovascular system. The lack of species specificity and widespread occurrence in the animal world suggest that it should have biologic significance.

We gratefully acknowledge the assistance of all those who have helped with these studies.

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The jugulocardiogram, an aid in the diagnosis of cardiac arrhythmias

It is well known that the electrocardiographic diagnosis of supraventricular versus ventricular tachycardia may be difficult or impossible in many cases because of (1) the occurrence of supraventricular tachycardia with concurrent bundle branch block or aberrant ventricular conduction, (2) failure of carotid sinus pressure or other methods of vagal stimulation to influence the arrhythmia, and (3) the absence of clearly identifiable P waves, capture beats, or fusion beats in the conventional electrocardiogram. Because of the essential difference between the prognoses and types of treatment in these arrhythmias, it has been necessary to employ special methods, such as the esophageal lead and the percutaneous intracavitary lead. Both of these techniques have certain obvious inherent disadvantages, ie difficulty in passing the esophageal lead in uncooperative or unconscious patients, and the dangers of coiling or knotting of the lead wire, and ventricular fibrillation due to improperly grounded equipment in the case of the intracavitary electrode.

The primary purpose of these special methods is to enhance the registration of P waves, since the key to the differential diagnosis of most cardiac arrhythmias lies in an appreciation of atrial activity and its relation to ventricular activity Thus, in differentiating supraventricular and ventricular tachycardias, an important diagnostic point is whether there is a regular relationship between P and QRS (supraventricular tachycardia), or whether there is A V dissociation (ventricular tachycardia)

An exceptional case of ventricular tachycardia with retrograde (V A) conduction[1] may be impossible to differentiate from nodal tachycardia with retrograde P waves in the presence of abnormal QRS complexes. Similarly the rare occurrence of nodal tachycardia with aberrant conduction and A-V dissociation may be indistinguishable from ventricular tachycardia. In the main, however the electrocardiographic diagnosis of ventricular tachycardia (in the absence of fusion or capture beats) depends on the recognition of independent atrial activity in the form of regular P waves without relation to the QRS complexes.

Since Mackenzie's original polygraphic studies, the jugular venous pulse has been known to be of value in the clinical differentiation of cardiac arrhythmias by revealing right atrial activity How

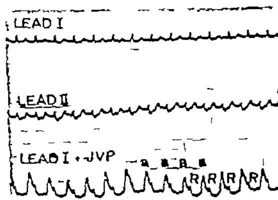


Fig 1 The upper two strips show Leads I and II of the electrocardiogram. The QRS duration is 0 12 sec in Lead II The rhythm is perfectly regular at 160 per minute No P waves, fusion beats, or captures are seen. The bottom strip is combined Lead I electrocardiogram and jugular venous pulse tracing (jugulocardiogram), showing regular prominent a waves preceding each R wave The a waves originate immediately after the wave which corresponds in time with the T wave of Lead I Thus, a P wave must be contained within the T wave and the diagnosis is, therefore atrial tachycardia with 1 1 conduction and first-degree A V block.

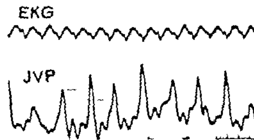


Fig 2 Top Lead I electrocardiogram showing a perfectly regular tachycardia at 200 per minute. The QRS interval is 0.12 sec P waves are not definitely identifiable. There are no fusion beats or captures *Bottom* Jugular venous pulse tracing showing regular independent a waves at 130 per minute The presence of A V dissociation is presumptive evidence of ventricular tachycardia.

ever it is surprising how often this simple physical diagnostic technique is neglected, probably because of ineffective methods of bedside teaching In previous communications, simple methods of facilitating clinical inspection and graphic recording of the jugular pulse have been described. [4] Subsequently this method of recording has proved to be of considerable utility in the diagnosis of arrhythmias.

The method consists of monitoring with a photocell the movements of a tab indicator taped to the neck at the point of maximal jugular pulsation The photocell wires are connected in series or in parallel with the patient and the electrocardiograph thus recording the electrocardiogram and the jugular pulse simultaneously This combined tracing or "jugulocardiogram," allows accurate timing of the venous waves with respect to the R wave of the electrocardiogram The position of P waves in the tracing may be inferred, since the a wave of atrial systole must be immediately preceded by atrial depolarization.

Figs 1 and 2 present illustrative arrhythmias. The advantages of the "jugulocardiographic" method are simplicity safety low cost, and acceptance by the patient A further advantage is portability since the necessary equipment excluding the electrocardiograph can easily be carried in the physician's bag

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Book reviews

HYALURONIDASE: AN ANNOTATED BIBLIOGRAPHY 1940-1955 By Myer M Fishman Ph D Associate Professor of Chemistry City University of New York. River Edge N J., Technical Service Laboratories 79 pages. Price $5.

This annotated bibliography by Dr Myer Fishman and the research staff of the Institute of Cancer Research of the College of Physicians and Surgeons of Columbia University is extremely useful for those interested in hyaluronidase It is a 79-page list of titles with concise summaries in one to three or four sentences which are very informative and well conceived This is a very valuable publication.

COMPARATIVE BASIC CARDIOLOGY By Jane Sands Robb M.D Sc.D., New York, 1965 Grune & Stratton Inc., 602 pages. Price $39

This book is primarily of interest to anatomists, physiologists, biologists, and research cardiologists. The author presents much too briefly an extensive coverage of the heart in all animals In so doing a great deal of the material is grossly inadequate to be of value to the reader For example in the chapter on gross anatomy of invertebrate hearts, Dr Robb discusses the *Lepidoptera* in a short paragraph and says nothing about the gross anatomy of the heart She merely discusses uncritically the electricity of conduction of impulses observed by Tenny and refers to the work of three other investigators by stating simply that they present the circulation more completely " Dr Robb does not indicate their findings on the circulation of the *Lepidoptera* and thus fails to help the reader of her book. The order *Orthoptera* is likewise poorly discussed, in spite of the fact that much is known of the circulation of insects of this order Dr Robb does, however include a extensive bibliography 72 pages of references. There is a large number of color plates in a color atlas appended to the book. Unfortunately the photomicrographs fail to present sufficient detail to be useful to the student of comparative anatomy of the heart. The author refers to red non-striated fibers and "red fiber " (Fig XII 8 and Fig XII 9) which is very loose terminology By this she apparently means that the fibers stained red with the stain used, but the fibers are not necessarily red non-striated fibers

There are some interesting aspects to this book and anyone who is interested in comparative anatomy of the heart can certainly find some useful information in it but for detailed information he will have to study the original papers.

HEART DISEASE IN CHILDREN By Benjamin M Gasul, M D., Rene A. Arcilla M D and Maurice Lev M D Philadelphia 1966 J B Lippincott Company 1363 pages. Price $33

This is a very good book by authors who are well known in the field of pediatric cardiology Unfortunately Dr Gasul did not live to see the completed publication of this testimonial to his many years of hard work. The book includes chapters on anatomy embryology history taking and physical examination, roentgenographic procedures, electrocardiography vectorcardiography arrhythmias, cardiac catheterization, and all the common diseases of the heart encountered in pediatric practice The illustrations are many and good and many references are appended to each chapter The book is organized like any standard textbook Written for students, general physicians pediatricians, and cardiologists it represents one of the best books available today in pediatric cardiology It is highly recommended

EXPERIMENTAL ATHEROSCLEROSIS. By Paris Constantinides M D Ph.D Professor of Anatomy University of British Columbia Medical School Vancouver B.C Canada Amsterdam and New York, 1965 Elsevier Publishing Co. 91 pages 103 illustrations, 2 colored plates and 8 tables. Price $11 50

During the past 10 years, important advances in producing atherosclerosis have been made Recently it has become possible in certain laboratory animals to reproduce the lesions and complications of human atherosclerosis The first part of this small monograph is devoted to a summary of human atherosclerosis This includes word and pictorial descriptions from the earliest recognizable lesions to the most advanced Atherogenesis is discussed in regard to the main current theories. The remainder and main part of the text deals with the methods used and results obtained in attempting to cause atherosclerotic lesions and their sequelae in animals Because of their marked susceptibility to the production of atherosclerosis through lipemia or arterial injury rabbits were used for the major portion of the author's work. The utilization of several other species for the purpose are mentioned in varying detail Point-by-point comparison is made between the findings in human atherosclerosis and in the experimentally produced lesions and complications These are also illustrated by ample line drawings and photomicrographs, which occupy the last quarter

of the book. The bibliography contains 433 citations.

This book is well written and illustrated. It should be of considerable use to those interested in the subject.

Congestive Heart Failure. By Raymond T. Benack, M.D., Clinical Instructor in Medicine, Georgetown University, Washington, D. C. Springfield, Ill., 1966, Charles C Thomas. 117 pages. Price $5.50.

Benack has reviewed the problem of congestive heart failure for the medical student and general practitioner. The epidemiology and a part on the community and the problems associated with congestive heart failure are the outstanding aspects of this book. This reflects the author's interests. The book is divided into seven chapters which deal with the prevalence, etiology, organ pathology, clinical manifestations, criteria for diagnosis, therapy of, and community programs for congestive heart failure. A good bibliography is included. The book is clearly written and easy to read and should be of interest even though only a few selected aspects of congestive heart failure can be expected to be found in a 117-page book on such a complex subject. The reader will find many interesting things in the book but he cannot expect to become an expert on the subject if he limits his reading to this short monograph.

Textbook of Medical Physiology. By Arthur C. Guyton, M.D., Professor and Chairman, Department of Physiology and Biophysics, University of Mississippi School of Medicine, ed. 3. Philadelphia, 1966, W. B. Saunders Company. 1210 pages. Price $16.

This third edition of a good and simplified book contains the necessary revisions to maintain an up-to-date textbook in physiology. The book is well written and nicely illustrated in a diagrammatic manner that is particularly useful to medical students and beginners in physiology. Dr. Guyton presents the fundamental principles of physiology clearly and accurately. The discussions are made simple in the interest of teaching. Obviously, the reader will find it necessary to study the medical literature carefully for detailed information of many of the complex physiologic phenomena which were oversimplified in the interest of teaching. Not only will medical students find the book useful, but so will all physicians in medicine who wish to maintain a clear knowledge of physiology. This book is recommended as one of the best in the field.

Pharmacology of the Coronary Circulation. By Natalia V. Kaverina, Head of the Laboratory of Cardiovascular Pharmacology, Institute of Pharmacology and Chemotherapy of the Academy of Medical Sciences, U.S.S.R. New York, 1965, Pergamon Press, Inc. 267 pages. Price $12.50.

This book summarizes briefly the point of view of one of the outstanding Soviet pharmacologists concerning the pharmacology of the coronary circulation. Dr. R. Crawford has translated the Russian very well. Consequently, the book is easy to read. It is divided into three parts, one on the present position of the physiology and pharmacology of the coronary circulation, another on the effects of pharmacologic substances on peripheral control of the cardiac circulation, and the third on the effects of pharmacologic agents. The well-known agents are discussed and reports from Soviet as well as from other laboratories of the world on studies of the actions of these agents are included. As would be expected, there is considerable difficulty in extrapolating studies in experimental animals to man with coronary disease and especially those with angina pectoris. This is clearly reflected on pages 191 to 215. Studies of the effects of nitroglycerin on the coronary circulation of dogs have produced conflicting reports, especially when the investigators attempt to apply their findings to man with ischemic heart disease. Some of the recent studies with coronary angiography are not included in the book, however. Nevertheless, pharmacologists, physiologists, and clinicians will find this book to be interesting and a fairly good brief summary of the present state of knowledge.

Books received

Fundamentals of Clinical Hematology. By Byrd S. Leavell and Oscar A. Thorup, second edition. Philadelphia, 1966, W. B. Saunders Co. 597 pages. Price $12.50.

The Cell. An Atlas of Fine Structure. Its Organelles and Inclusions. By Don W. Fawcett, M.D. Philadelphia, 1966, W. B. Saunders Co. 448 pages. Price $11.

Ozaena. A Manifestation of Iron Deficiency. By Ivan Bernat, translated by Miss Esme Hadfield. Long Island, N. Y., 1965, Pergamon Press. 116 pages. Price $3.

Herman Carel Burger

Herman Carel Burger to whom cardiology owes a new and fruitful approach of fundamental importance to both vectorcardiography and ballistocardiography died after a short illness on Dec 28 1965 less than a year after the loss of his wife

He was born in Utrecht on June 1 1893 and he worked and lived in Utrecht or its immediate neighborhood nearly all of his life As a boy he was already greatly interested in science and impressed his teacher who worked as a physicist in the University s department of physiology so much that he left his library to Burger With the help of a friend who happened to be the son of a pharmacist he undertook experiments in chemistry and together with his younger brother spent *much time in botanical field work.*

Languages were not his real interest but when he was forced by the then existing rules of admission to the university to pass an examination in Greek and Latin he did so in an unusually short time. However to celebrate his admission he made a bonfire of his Greek and Latin textbooks.

This tendency to concentrate on the main subjects of his interest and to set aside all other things continued to show itself during the rest of his life. Music and literature were not for him although his interests in science were wide and varied

On leaving high school he had some hesitation in choosing between the study of physics and of medicine. Later this interest in medicine was to manifest itself more fully but for a long period it did not become apparent

Burger graduated in Utrecht and stayed on as an assistant in Ornstein s laboratory He took his Ph D in 1918 his subject was the formation of crystals. In the following 20 years with an interruption of only 2 years in which he worked as a research physicist in the Philips factories in Eindhoven he continued to do research in pure physics in Utrecht mainly on quantitative spectral analysis, one of the most important research projects of the Utrecht school of physics at that time.



Herman Carel Burger 1893-1965

In 1927 he was given the position of reader with the assignment of introducing the students in medicine biology dentistry and veterinary surgery to physics. Although his research remained in the field of pure physics, he showed his concern for medicine by carefully adapting his course to the needs of the medical students, which was by no means customary

Gradually his scientific interest began to shift to medicine however and his first paper on a medical subject (i.e. the electrical conductivity of the human body) appeared in 1941. When later on during the war research was no longer possible Burger applied himself to the study of human physiology. In this way he prepared at the age of 50 for his second career that in medical physics.

Soon after the end of the war (from 1946 on) a series of papers on vectorcardiography began to appear in which Burger led cardiology back to the physical basis of the method which since Einthoven's time had too often been neglected. He also put against Einthoven's equilateral triangle (a simplification of which Einthoven himself was well aware) the generally applicable case of the asymmetrical triangle which continues to bear his name. He did this in a very lucid and concise way with as little mathematics as possible knowing full well that the medical public usually shies away from mathematical formulae. This point was later repeatedly stressed by him and was of paramount importance in his relationships with medical men.

Another fundamental contribution was made by Burger in the field of ballistocardiography. Here again he examined the physical basis of the method and made clear that the essential feature under examination was the displacement of the blood inside the body. Therefore the method employed had to record displacement and to this end he revived the low frequency ballistocardiograph. At the same time he made clear that other existing methods were registering the first and second derivatives of displacement (velocity and acceleration respectively). Always looking for conciliation without vague compromise he was quick to point out that this difference in method could be easily overcome by simple mathematical and electrical means.

Burger did not limit his activities to these two main issues. In his laboratory the effect of stenosis on blood flow and the distribution of dye after injection into the blood stream were studied as well as the physical basis of auscultation and percussion to name only the most important subjects.

In the course of the years he literally created medical physics in his own country and gave cardiology throughout the world the support of a firmer basis in physics. He was the first Professor of Medical Physics in Holland and served as a member of both the faculty of natural sciences and the faculty of medicine. This seems to have been characteristic enough of a man who more than anybody else was concerned with cooperation and mutual understanding between physicists and medical doctors. His work for the development of medical physics and of cardiology was acknowledged by the conferring of an honorary degree by the University of Nymegen and by the invitation to deliver the Einthoven Lecture in Leiden in 1962.

His role as a coordinator between physics and medicine was greatly helped indeed made possible by his remarkable and very human personality. To meet Burger and to discuss with him was to like him and to admire his never wavering search for the exact truth and the really clear way of expressing it as well as his absolute honesty and modesty which were associated with a fierce contempt for falsity and meaningless phrases.

Nowhere were these qualities better demonstrated than in the Dutch Biophysical Society which in its almost 20 years of existence before the war had confined itself to the organization of symposia. Burger who became president after the end of the war transformed this society into a highly active organization consisting of several discussion groups on various subjects, in each of which both physicists and medical experts took part. For many Dutch cardiologists this was an unforgettable experience and the Biophysical Society still follows the same successful pattern.

It is above all in this way that the brilliant and skillful physicist who succeeded in fulfilling his own dual interest in physics and medicine by the fertilization of cardiology with the concepts and exactitude of physics will be remembered by his many friends. They will continue to think of him with gratitude and affection.

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Editorial

Coronary artery visualization and coronary surgery—A word of caution

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*Martial A. Demany, M.D.***
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No one will deny the advance in the study of the coronary arterial tree by selective cine-coronary-arterial visualization and the resulting clear outlines of large vessel disease in the form of narrowing, constriction, obstruction, and anomalies, and in the demonstration of collateral vessels.

However, to say that the above-mentioned technique relegates the electrocardiogram to a place in the Smithsonian Institute, as was said at a recent panel discussion, should not be allowed to pass without comment.

Cine-coronary arteriography has very definite limitations as now carried out:

1. It tells nothing of the small coronary arterioles or small vessels, and to deny or dismiss the fact that disease occurs in these vessels is without foundation. One has only to compare a postmortem injection of the coronary arterial tree with a barium latex mixture of standardized particle size with a cine-coronary arteriogram to see literally hundreds of vessels which are not studied by this technique. Also, very early disease cannot be found or documented by the present technique.

2. Cine-coronary arteriography tells one nothing about coronary arterial flow; that a vessel can be injected and seen does not necessarily mean that any significant perfusion of a myocardial segment is being carried out. Nor does a 50 per cent narrowing mean that flow is necessarily diminished. Measurement of differential coronary flow must be devised to supplement this technique.

3. The technique tells one absolutely nothing about what is occurring at the cellular level. To determine the latter may well prove to be the most profitable approach to the study of the coronary circulation. Cineangiocardiography may show one to have excellent coronary arteries, but the myocardium may be studded with fibrosis and there may be advanced myocardial disease. A case in point is that of a 46-year-old pilot who is found at the time of his yearly physical examination to have a left bundle branch block; this finding was not present on previous examinations. Selective

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coronary arteriography is carried out and his coronary arteries appear to be perfectly normal. However, a left ventricular end diastolic pressure of 28 mm. Hg is recorded. He is told on the basis of normal cine-coronary arteriography that his heart is perfectly normal and he is allowed to continue to fly. It should be quite obvious that the pilot must have primary myocardial disease which is giving rise to the left bundle branch block and elevated left ventricular end-diastolic pressure.

4. The technique is not without danger and may be catastrophic. There are reports of ventricular fibrillation and deaths from selective cineangiocardiography. Even a reversible ventricular fibrillation is not to be taken lightly. Strict attention must be paid to meticulous technique if one is to avoid serious complications. There have been no deaths in our series of 275 patients who have undergone coronary cineangiocardiography, nor has there been any incidence of ventricular fibrillation. The reason for this has been our strict attention to technique and to the type of contrast medium used (60 per cent Renografin* which incidentally has a much lower sodium content than any of the other contrast agents which are used).

5. As for radiation hazard, very little attention has been paid to the rather large doses of x ray which are directed to the patient's heart in the making of multiple selective coronary visualizations. Conservative estimates of total radiation to the patient's heart during a procedure approximate 40 to 80 roentgens in our laboratory. (One 6-foot chest x ray film averages .007 roentgens.) What the physiologic results are from the irradiation to the heart in an acute form and on a long range basis have not, to our knowledge, been studied.

6. Injury to the brachial artery and radial nerve, with resulting morbidity, is a final consideration.

Hence coronary arterial visualization is not to be taken for granted. Its use must have a good basis in sound clinical judgment.

The same can be said for the reports of brilliant results with operations to improve coronary circulation. At the moment, to our knowledge, no sound and proved studies have been carried out in human beings to show the benefits derived from the numerous procedures now being applied to revascularize the human heart.

Confusion is rampant. Recently, a cardiac surgeon made the statement that he had never seen sclerosis of the internal mammary artery and added that sclerosis does not exist in this artery. A few weeks later, another cardiac surgeon of equal prestige stated that he had abandoned internal mammary transplants because of the existing sclerosis in the internal mammary artery. And still another one told of his operation perfusing the coronary arterial tree hours after surgery, and he presented cineangiograms to prove his contention.

No one knows at the moment how much flow is added to the coronary circulation, nor, for that matter, what is the normal flow of blood through the internal mammary artery.

Even with added flow to the large vessels, how much of this becomes available for cellular perfusion, how much runs off through large connecting channels which add nothing to cellular perfusion?

Do revascularization procedures of the myocardium add anything to the present management of coronary artery disease? Reminiscent are the operations of poudrage and ligation of the internal mammary arteries.

Can the same revascularization and collateralization of circulation occur by a regulated regimen of exercise?

Is it necessary to provide an exercise program for patients who have undergone revascularization procedures, in order to bring about or to develop a collateral circulation?

What is the rate of sclerosis in the anastomosed or implanted vessel? For that matter, what is the rate of development or progression of sclerosis in a coronary artery?

Only controlled and well planned studies carried out in patients, not studies in the dog or pig, can answer the foregoing and many other questions covering the intriguing and elusive coronary circulation, and this will take years to accomplish. Until then, a word of caution.

*E. R. Squibb & Sons, New York, N. Y.

Clinical communications

Leftward shift of the terminal P forces in the ECG associated with left atrial enlargement

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The currently recognized criteria for the electrocardiographic diagnosis of left atrial enlargement (LAE) include (1) P mitrale (a notched P wave exceeding 0.11 second in duration),[1-4] (2) a large negative P deflection in Lead V_1,[4-7] and (3) a left axis shift of the P vector in the frontal plane.[8-9] This report presents an analysis of P axis shifts in patients with and without heart disease and correlates them with coexisting criteria of LAE. The initial and terminal components of the P forces are analyzed and their clinical diagnostic value is determined.

Material and methods

From the files of the George Washington University Hospital Heart Station, the electrocardiograms of 700 consecutive patients with a diagnosis of heart disease were selected for the study. There were 308 males and 392 females with an age range from 18 to 86 and a mean age of 48 years. Their electrocardiograms were examined for leftward shifts of the P axis (mean initial and terminal) in the frontal plane. Thirty cases were found, 2 with left axis deviation of the mean P wave and 28 with leftward axis shift of only the terminal portion of the P. These 28 cases will be described in detail.

The average age for the group was 48.4 years. There were 11 males with an average age of 54.6 years, and 17 females with an average age of 44.4 years. The clinical diagnosis in this latter group of patients was as follows: 13 (46 per cent) had isolated mitral stenosis, 3 (10 per cent) had combined mitral stenosis and insufficiency, 3 (10 per cent) had combined mitral and aortic valve disease, 4 (14 per cent) had aortic stenosis, and 5 (18 per cent) had

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coronary artery disease with chronic congestive heart failure. Twenty-three patients (82 per cent) had valvular heart disease and 5 had nonvalvular heart disease. Hospital records were examined for evidence of LAE; there were autopsy data in 4 of these. In 24 of the 28 cases in the present series, nonelectrocardiographic evidence supported the presence of LAE: open-heart surgery for mitral valvotomy in 14 cases, autopsy and x-ray films in 4 cases, and x-ray films alone in 6 cases. In the other 4, x-ray films were not available for study, but the presence of chronic congestive heart failure suggests the possibility of LAE.[4]

The control group, with records also from the Heart Station files, consisted of 500 consecutive patients without a diagnosis of heart disease. The electrocardiograms of these patients were similarly examined for P abnormalities.

Although a wide range of values of the P axis has been described as normal, there is agreement that an orientation toward the positive pole of Lead II (+60 degrees) represents a normally directed axis.[1,7,15,19] The mean initial and terminal axes were calculated in the frontal plane and plotted on the hexaxial figure according to the method of Grant.[1] This method of measurement of axes is considered to have a limit of accuracy of approximately 15 degrees.[9] The first portion of the P wave *in the lead with maximal P duration* was considered to represent the initial P forces, whereas the second portion of the P in the same lead was considered to represent the terminal forces.[1,16]

The morphology of all P waves was

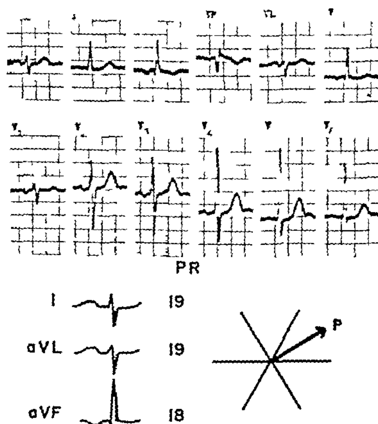


Fig. 1. Electrocardiogram of patient with mitral stenosis showing a mean P-wave axis of −30 degrees. Initial and terminal forces do not diverge. In Leads I, aVL, and aVF are diagrams of the P and QRS complex. Note that there is little difference between the P-R intervals in these leads.

Table I Tabulation of clinical and ECG data on 28 patients with left shifts of the terminal P axis*

Case No.	Age Sex	Diagnosis	Frontal plane: Mean P axis	Frontal plane: Initial P axis	Frontal plane: Terminal P axis	Frontal plane: Angle between I and T	Frontal plane: P-R (sec) in II-aVF	Frontal plane: P-R (sec) in aVL or I	Negative P in V1: Amplitude (mm)	Negative P in V1: Duration (sec)	Negative P in V1: Left atrial force†	Negative P in V1: Abnormal left atrial force‡	P notching
1	67 M	CHD CHF	60°	90°	−20	110°	0 20	0 16	05	0 06	03		+
2	64 M	AS	60	70	5	65	0 14	0 08	16	0 06	096	+	+
3	60 F	AS	40	75	−10	85	0 18	0 13	01	0 06	02		+
4	56 F	AS	70	70	−10	80	0 18	0 13	04	0 06	02		
5	57 M	AS	60	80	5	75	0 14	0 09	03	0 04	01		
6	12 F	MS, AI	60	75	20	55	0 16	0 12	05	0 03	025		
7	59 F	MS	70	75	5	70	0 18	0 14	07	0 06	04	+	+
8	32 M	AS AI MS	60	70	10	60	0 18	0 14	10	0 06	06	+	
9	48, F	MS MR	65	75	0	75	0 21	0 14	05	0 06	03		+
10	29 F	MS	70	75	10	65	0 14	0 09	03	0 01	01		
11	41 F	MS	50	85	0	85	0 20	0 15	11	0 04	04	+	+
12	38, F	MS	60	80	20	60	0 16	0 11	0	0 00	0		+
13	43 F	MS	50	70	−5	75	0 14	0 11	10	0 06	06	+	
14	58, F	MS MR	40	70	10	60	0 17	0 12	12	0 05	06	+	+
15	65 M	CHD CHF	70	80	20	60	0 20	0 15	05	0 03	015		+
16	41 F	MS, MR	60	70	0	70	0 17	0 14	12	0 04	05	+	+
17	40, M	AS, AI MR	60	80	30	50	0 20	0 13	10	0 06	06	+	
18	68, F	MS	60	70	−5	75	0 17	0 13	07	0 06	04	+	
19	37 F	MS	60	75	−10	85	0 17	0 13	13	0 05	065	+	
20	42 F	MS	70	75	0	75	0 17	0 13	0	0 00	0		
21	37 M	MS	60	70	0	70	0 16	0 11	06	0 03	02		
22	32 F	MS	60	70	−5	75	0 17	0 11	15	0 06	075	+	+
23	42 M	MS	60	70	5	65	0 22	0 16	15	0 06	075	+	+
24	30 F	MS	50	70	−5	75	0 11	0 10	09	0 04	036	+	
25	41 F	MS	60	65	5	60	0 22	0 16	10	0 05	05	+	
26	67 M	CHD CHF	40	80	−40	120	0 16	0 12	03	0 04	01		
27	63 M	CHD CHF	70	90	0	80	0 17	0 12	08	0 05	04	+	+
28	67 M	CHD CHF	60	80	10	70	0 21	0 15	04	0 06	02		
	11 M 17 F		59 1	74.8	1 6	73.2	0 174	0 126				15	13

*Note that the P-R is shorter in Lead I or Lead VL than in Lead II or Lead VF and that the mean P axis in the frontal plane is normal.
†As defined by Morris and associates.
‡If the product of amplitude in millimeters and duration in seconds is > 0.03, it is considered to be abnormally large.

noted and measurements were made of amplitude and duration in the 12 leads. The P R intervals were also measured The magnitude of the negative deflection of the P in Lead V_1 has been quantitated by Morris and associates[4] and termed atrial force which is the product of the amplitude in millimeters and the duration in seconds this is considered to be abnormally large if it exceeds 03 We have followed the above mentioned PV_1 criterion as an indication of LAL

Results

A Cardiovascular disease group Among the 30 cases with abnormal leftward shifts of the P wave 2 patients both with mitral stenosis had a mean P axis of −30 degrees (Fig 1) In these the P wave was isoelectric in Lead II and maximal in Lead aVL There was no significant divergence between initial and terminal forces The negative deflection of the P in Lead V_1 was abnormally large in both

In 28 cases (see Table I) the leftward shift of the atrial axis was limited to the terminal portion of the P wave The mean axis of the P wave varied between +40 and +70 degrees with a mean for the group of +59 1 degrees. The mean axis of the initial P forces was +74 8 degrees for the entire group with a range of +65 to +90 degrees and the mean axis of the terminal P forces was +1 6 degrees with a range of +30 to −40 degrees (Fig 2) The mean angle between initial and terminal forces was 73 2 degrees, with a range of 50 to 120 degrees. Only 3 cases had an angle between initial and terminal forces of less than 60 degrees. In 4 the terminal force was intermediate in location (3 with +20 degrees and one with +30 degrees)

The diverging initial and terminal P forces are usually reflected in the electrocardiogram by diphasic P waves. Lead III shows a positive negative morphology and Lead aVL shows a negative-positive morphology Also the initial portion of the P in Lead aVL may be isoelectric and thus suggest a shortening of the P R interval in that lead (Fig 3) Lead I may also suggest shortening of the P R when the initial P axis is oriented toward +90 degrees.

Only 13 (46 per cent) of these 28 cases had a P mitrale in the limb leads The mean duration of the broadest P was 0 11 second (range 0 07 to 0 13 second) and the mean of the greatest amplitudes was 0 11 mv (range 0 05 to 0 18 mv)

Fifteen (54 per cent) cases had a significant negative deflection of the P wave in Lead V_1 indicating LAE. In the 8 cases with neither P mitrale nor a large negative P in Lead V_1 left axis shift of the terminal P was the only ECG indication of LAE.

B Control group The control group comprised 218 males and 282 females with an age range from 21 to 79 and a mean age of 44 years. The mean P axis for this group was +60 degrees 15 (3 per cent) had a mean P axis between 0 and +30 degrees. None had an axis to the left of 0 degrees. In 75 electrocardiograms (15 per cent) diverging initial and terminal components could be identified This divergence was usually slight and accurate measurement of the component axes was often impossible. The initial and terminal components were not usually separated by more than 40 degrees and only one patient had terminal P forces to the left of +30 degrees. This patient, a 58-year-old man with cerebral thrombosis had an electrocardiogram with widely diverging initial and terminal axes (0 and +70 degrees, respec

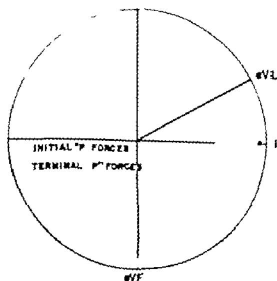


Fig 2 Scattergram showing initial and terminal P forces (axes) in the frontal plane in the 28 patients with leftward shifts of the terminal P

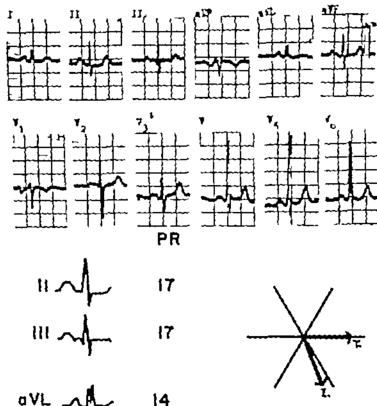


Fig 3 Electrocardiogram of patient with mitral stenosis (Case No. 16), showing leftward shift of terminal P to 0 degrees in the frontal plane. Note that the P R interval is shorter in Lead aVL than in Leads II and III

tively) and no clinical evidence of heart disease. The cause for the leftward shift of the terminal P force in this man was not determined.

Discussion

The electrocardiographic recognition of LAE has been well established in regard to the prolonged notched P mitrale. Also the prominent negative P deflection in Lead V1, caused by a posterior rotation of the left atrial vector in the horizontal plane, is well known. Little attention has been paid to the less frequent axis shifts of component initial and terminal P forces in the frontal plane. When this P change was noted by others it has been characterized as "left axis deviation of the P wave in spite of a normally directed initial and mean P axis[1, 4-11] The limits of normal initial and terminal P axes have not been established In one series, involving the electrocardiograms of 67 375 asymptomatic adult males, less than 10 per cent had a mean P axis to the left of +30 degrees.[15] It seems to be more appropriate to use the term leftward shift of the axis to indicate a leftward change as compared to its own initial or mean axis and to limit the term left axis deviation to describe axes between 0 and −90 degrees

Although left axis deviation of the terminal summit of the P mitrale has been mentioned by others,[13,16] the diverging initial and terminal forces may be smoothly merged in leads showing both components and thus a P mitrale morphology may not occur [18]

The possible presence of an ectopic atrial pacemaker in the cases with mean P axis (initial and terminal axes) in the region of −30 degrees may limit the usefulness of using the mean P axis as a guide to the presence of LAE. In our 2 cases with this type of P-axis change both showed other ECG and clinical evidence of LAE. A shift of both components of the P wave to the left cannot be expected in cases of

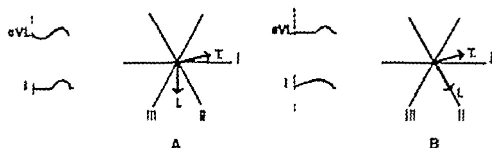


Fig. 4. Diagram of P waves in Lead I and aVL and the initial and terminal P wave forces on the triaxial system. Note the effect of direction of initial P wave forces on shortening (isoelectric period) of the P-R interval in Lead I (A) and Lead aVL (B).

biatrial enlargement because of the tendency of right atrial enlargement to shift the axis in a rightward direction.

The use of a shorter P-R interval in Lead aVL is based on the concept of an isoelectric period[9] in that lead being caused by initial forces which are parallel to the positive pole of Lead II. If the initial forces are oriented appreciably to the right of 60 degrees a diphasic P wave with an initial negative deflection is expected in Lead aVL. In this event the isoelectric initial component and the shorter P-R interval might be expected in Lead I (Fig. 4). Therefore a shortened P-R interval limited to either Lead aVL or Lead I indicates a divergence of terminal forces from the more normally directed initial P forces. Only the terminal or left atrial forces are directed toward the positive poles of these leads.

The factors related to rightward shifts of the initial P forces are poorly understood although some of these are undoubtedly related to right atrial enlargement.[18]

In marked enlargement of the left atrium "giant left atrium" marked left axis deviation or even a shift in axis to the right might be expected because of distention of that chamber into the right hemithorax. However this condition is usually associated with atrial fibrillation[22] and the value of P-axis determination is thereby lost.

The frontal plane P loops in patients with P mitrale as displayed on the vector cardiogram (VCG) may show the same leftward direction of the terminal forces.[2,24] However accurate analyses of the P wave using standard VCG techniques is difficult because of the small size of the P loop and spatial interference by the superimposed QRS and T loops.

Summary and conclusion

The electrocardiograms of 700 patients with cardiovascular disease and 500 subjects without such disease were screened for leftward shifts of the P axis. Such shifts were found almost exclusively in the electrocardiograms of 30 patients with heart disease; in all there was evidence of left atrial enlargement. In 2 the entire P wave had left axis deviation. In 28 cases there was a leftward shift of only the terminal forces of the P. In the control group only one subject showed leftward shift of the terminal P forces. This may be recognized by a late positive P deflection in Lead aVL or Lead I or a negative deflection limited to the terminal portion of the P in Leads III or aVF. This divergence of initial and terminal P forces of more than 40 degrees in the frontal plane is due to a leftward shift of the terminal forces and is the most frequently found leftward axis shift. In 8 of the 30 patients this P change represented the sole ECG indication of left atrial enlargement.

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Alveolar-arterial oxygen tension gradients in cirrhosis of the liver

Further evidence of existing pulmonary arteriovenous shunting

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Peripheral arterial desaturation in patients with cirrhosis of the liver was first recognized by Fluckiger[1] in 1884. This finding was believed to represent a shift to the right of the oxyhemoglobin dissociation curve.[2] The affinity for oxygen of the hemoglobin molecule was found to be normal,[3] and the observed arterial desaturation was ascribed to the presence of venoarterial admixture.[4]

The site of venoarterial admixture is still not settled. In the juvenile type of cirrhosis of the liver, the shunting of blood occurs in the pulmonary arteriovenous anastomoses which were demonstrated at postmortem by Rydell and Hoffbauer.[5] In acquired adult cirrhosis, portal vein-to-pulmonary vein vascular communications were demonstrated.[6] The shunting of blood through these channels was assumed to be responsible for the observed arterial desaturation.[7] In a previous report,[8] we postulated that these two anatomic sites of venoarterial admixture may be operating simultaneously in patients with cirrhosis of the liver, but that the pulmonary site was the primary factor in the production of hypoxemia.

The purpose of this study was to examine alveolar-arterial gas exchange in patients with cirrhosis of the liver and to evaluate the effects of moderate exercise and of portacaval anastomosis on the alveolar-arterial oxygen tension gradients.

Materials and methods

Twenty-six patients, 20 men and 6 women, with cirrhosis of the liver were studied. Their ages ranged between 44 and 68 years and averaged 54.4 years. Initially, in all of these patients the pulmonary gaseous exchange was determined while they were resting in a supine position breathing ambient air; then these studies were repeated in 5 patients (Cases 1-5) after 15 minutes of continuous breathing of a low-O_2 mixture (15 per cent). In the other 21 patients (Cases 6-26) the studies were performed after a 30-minute period of breathing 100 per cent O_2 and then after 2 minutes of leg exercise while still breathing pure O_2.

The diagnosis of cirrhosis of the liver was made on clinical and laboratory grounds and verified by needle biopsy of the liver or at postmortem examination. All of

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these patients, with the exception of one (Case 19) had Laennec's cirrhosis. Case 19 had biliary cirrhosis.

In 4 patients (Cases 23-26) side-to-side anastomosis of the portal vein to the inferior vena cava was performed because of the repeated episodes of bleeding from esophageal varices. In all a marked drop in the portal vein pressure followed the anastomosis from 340 to 228 mm of citrate in Case 23 from 340 to 220 in Case 24 from 470 to 185 in Case 25 and from 470 to 220 in Case 26 These patients were studied 12 6 24 and 3 months, respectively after operation. At necropsy all 4 patients had patent portacaval anastomosis.

Alveolar-arterial gas exchange was determined in a control group of 11 hospitalized individuals with no evidence of liver dysfunction

Expired air was collected over a 3-minute period in a Douglas bag Oxygen and carbon-dioxide concentrations in the expired air were determined by the Beckman E 2 and Liston-Becker analyzers, respectively The respiratory quotient was measured in all patients at rest The oxygen and carbon-dioxide content of arterial blood was determined by the method of Van Slyke and Neill Arterial blood oxygen (PaO_2) and carbon-dioxide ($PaCO_2$) tensions were determined polarographically from the whole blood using the Clark electrode[9] This polarographic technique was previously described from this laboratory[11]

The alveolar oxygen tension (P_AO_2) was calculated from the alveolar air equation

$$P_AO_2 = P_IO_2 - P_ACO_2 \left(F_IO_2 + \frac{1 - F_IO_2}{R.Q}\right)$$

P_IO_2 represents inspired oxygen tension P_ACO_2 = alveolar CO_2 tension assumed to be equal to arterial CO_2 tension R Q = respiratory quotient F_IO_2 = fractional concentration of oxygen in the inspired air During the breathing of 100 per cent oxygen the correction factor included in the parentheses would be reduced to 1 regardless of the value of the respiratory quotient The alveolar oxygen tension would then be equal to

$$P_AO_2 = B - P_{H_2O} - P_ACO_2$$

where B = barometric pressure, P_{H_2O} = water vapor tension at 37°C = 47 mm Hg P_ACO_2 = alveolar carbon-dioxide tension assumed to be the same as arterial carbon-dioxide tension

The alveolar-arterial oxygen tension gradient or A a gradient is the arithmetic difference between the alveolar and the arterial oxygen tensions. In normal individuals, this A-a gradient on room air breathing is 13 ± 6 5 mm Hg[12] After ambient air studies were completed the patient breathed pure oxygen for 30 minutes. This would allow sufficient time for complete equilibrium between the alveolar air and the pulmonary capillary blood Under these conditions the A a gradient of less than 60 mm Hg is observed in the recumbent and resting normal individuals.[12] In this position and still breathing 100 per cent oxygen the patients exercised their legs either using a piston type exerciser or alternately raising their legs After 2 minutes, and while they were still exercising the alveolar arterial oxygen tension gradient was measured No attempt was made to determine whether a steady state was accomplished or to quantify the total oxygen consumption during exercise In separate studies at this level of exercise the oxygen consumption ranged between 400 and 800 ml per minute

Results

As seen in Table I the breathing of 15 per cent oxygen resulted in a moderate drop in both the arterial oxygen saturation and the A a gradient. The mean A a gradient decreased from 35 to 18 mm Hg

When they breathed room air patients with cirrhosis of the liver had a moderate degree of arterial desaturation with elevated A a gradient, as shown in Table II The mean systemic arterial oxygen saturation was 91 3 per cent. The mean alveolar arterial (A-a) oxygen tension gradient was 44 8 mm Hg and ranged between 23 and 75 mm Hg

The breathing of pure oxygen resulted in a large A a gradient in the majority of patients (in 16 of the 21 patients thus studied) The mean A-a gradient was 146 mm Hg and ranged between 13 and 466 mm Hg With the exception of 2 patients (Cases 6 and 14) leg exercise during the

Table I Study on arterial oxygen during the breathing of room air and the breathing of 15 per cent O_2 in patients with cirrhosis of the liver

Case	Room air		15 per cent O	
	O saturation (per cent)	A-a gradient (mm Hg)	O saturation (per cent)	A-a gradient (mm Hg)
1	94	25	90.6	15
2	92	24	89	9
3	93	31	90	18
4	80	50	72	22
5	89	46	8	28
Mean	89	35	84	18

breathing of 100 per cent oxygen further increased the A-a gradient that was obtained when the patient breathed pure oxygen. The mean increase in the A-a gradient was 61 mm Hg and ranged between −6 and +201 mm Hg. In 11 patients, exercise resulted in an increase of 40 mm Hg or more in the A-a gradient.

The effect of exercise on the A-a gradient in a control group of 11 individuals breathing 100 per cent oxygen is shown in Table III. In this group the PaO_2 during the breathing of 100 per cent oxygen ranged between 608 and 648 mm. Hg and the mean A-a gradient was 48 mm. Hg. When exercise was added the mean increase in the A-a gradient was 10 mm Hg and ranged between −14 and +36 mm Hg.

The results of pulmonary gaseous exchange in patients who had undergone successful portacaval anastomosis are shown in detail in Table IV. In Cases 23 and 26 studies were performed before and after operation. Preoperatively, Case 26 suffered several episodes of esophageal bleeding; at operation extensive deposition of iron particles was found in the liver.

Discussion

Altered exchange of pulmonary gases is the primary cause of hypoxemia in Laennec's cirrhosis.[14] This condition may result from (a) *Hypoventilation*. This is a factor that is rarely seen in the cirrhotic patient; on the contrary, low arterial PCO_2 is usually the case.[15] (b) *Impaired diffusion*. In alcoholics and in cirrhotics the tendency to develop recurrent pulmonary infections may result in pulmonary fibrosis and thickening of the alveolar membrane and a decrease in effective gaseous exchange. In such instances, breathing a low-oxygen mixture will increase the degree of hypoxemia. In Table I a decrease in the A-a gradient was observed which suggested and confirmed previous observation[14] that impaired diffusion did not play a significant role in the observed peripheral arterial desaturation in the cirrhotic patient. (c) *Abnormal ventilation perfusion relationship*. Disproportionate blood perfusion of underventilated lung tissue which may result from ascites interfering with ventilation or from intercurrent obstructive pulmonary disease could be the seat of pulmonary venoarterial admixture. Breathing 100 per cent O_2 corrects this state, unless (d) *the admixture is the result of direct venoarterial communication or nonventilation of segments with preserved blood flow*. A large A-a gradient is diagnostic of this state. This finding was observed previously by us[8] and confirmed by other investigators.[17-19] Since in this group of patients there was no evidence of intercurrent pulmonary disease that would be expected to be accompanied by areas of atelectasis or complete consolidation, complete nonventilation of perfused lung units is not likely to account for the major degree of venoarterial admixture observed here. On the other hand, such may be the case in those subjects in whom the gradient decreased during exercise with the breathing of 100 per cent oxygen. Exercise which is accompanied by deeper breathing could open previously closed lung units.

Two identified sites of direct venoarterial communications (namely, portopulmonary and pulmonary arterioles-to-venules anastomoses) were individually and singly implicated as the cause of hypoxemia in patients with Laennec's cirrhosis. Portopulmonary anastomosis, shunting portal venous blood directly into the pulmonary vein, was observed at necropsy in 2 patients with cirrhosis of the liver[4] and physiologically described by Fritts and associates,[7,20] using krypton 85 injected directly into the duodenum. The

Table II Pulmonary gaseous exchange in patients with cirrhosis of the liver at rest and during exercise

Case	Ascites	Room-air breathing		A-a gradient on 100% O breathing		
		SaO_2 (%)	A-a (mm Hg)	Rest	Exercise	Δ
6.	++	92	37	146	141	−5
7	+++	98	23	36	57	+21
8.	0	95	39	87	151	+64
9	0	93	46	43	110	+67
10.	+++	93	25	67	93	+26
11	0	95	—	87	105	+18
12.	0	92	48	308	408	+100
13.	0	91	41	82	274	+192
14	0	90	52	49	43	−6
15	0	99	27	13	27	+14
16	++	92	55	169	264	+95
17	++	93	41	40	111	+71
18.	+++	93	49	86	93	+7
19	0	92	29	76	117	+41
20	++	81	66	199	255	+56
21	0	80	75	466	610	+144
22.	0	83	47	185	273	+88
"Portacaval shunt"						
23b.	0	86	59	363	564	+201
24b.	+	90	49	371	394	+23
26b	++	95	43	54	62	+8
Mean		91.3	44.8	146.4	207.6	+61.2

*Calculated PaO_2.
b: Postoperative student.
Δ: Change in A-a gradient after exercise.
Ascites: 0 = None, + = Minimal, ++ = Moderate, +++ = Marked.

Table III Study on the alveolar-arterial oxygen tension gradient during the breathing of 100 per cent oxygen in the control group both at rest and during exercise

Case	100 per cent O_2 breathing alone		100 per cent O breathing and exercise	ΔExercise-rest
	PaO_2 (mm. Hg)	A-a gradient (mm Hg)	A-a gradient (mm Hg)	A-a gradient (mm Hg)
1	630	48	67	+19
2.	608	86	93	+7
3	609	58	86	+28
4.	613	62	71	+9
5.	648	31	18	−13
6.	631	39	74	+35
7	637	54	40	−14
8.	623	45	38	−7
9	633	43	43	0
10	644	32	42	+10
11	636	31	67	+36
Mean		48.1	58.1	+10
S.D.		±16.0	±22.1	

ΔExercise-rest: Change in A-a gradient after exercise.

Table IV. Pulmonary gaseous exchange in patients with cirrhosis of the liver after portacaval anastomosis

Case	Room-air breathing				100 per cent O_2 breathing alone		100 per cent O_2 breathing and exercise		ΔExercise-rest
	SaO_2 (per cent)	PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)	A-a gradient (mm Hg)	PaO_2 (mm Hg)	A-a gradient (mm Hg)	PaO_2 (mm Hg)	A-a gradient (mm Hg)	A-a gradient (mm Hg)
23a	83	49							
23b	86	57	37	59	311	363	110	564	+201
24b	90	73	31	49	308	371	287	394	+23
25b	94	80	31	43	293	384	—	—	—
26a	—	—	—	—	635	35	—	—	—
26b	95	78	4	43	627	54	617	62	+8

a Preoperative. b Postoperative. SaO_2, Systemic arterial O_2 saturation. ΔExercise-rest, Change in A-a gradient after exercise.

functioning of these anastomotic channels is presumably due to the development of portal hypertension. In such cases after surgical establishment of portacaval anastomosis the magnitude of venoarterial admixture would be markedly reduced if the portal venous blood is shunted away from the pulmonary vein to the inferior vena cava. In our cases the immediate reduction in the portal vein pressure that was observed at operation would indicate a diversion of portal venous blood to the inferior vena cava had occurred. In Cases 23, 24, and 25 (Table IV) large A-a gradients were observed during the breathing of 100 per cent oxygen after portacaval anastomoses, corresponding to 20, 21, and 22 per cent of their respective cardiac outputs as estimated from the alveolar-arterial O_2 tension gradients on 100 per cent oxygen breathing and an arteriovenous O_2 content difference of 4.3 volumes per cent.[22] It is inconceivable that such a large shunt which theoretically approximates the total splanchnic blood flow is in operation between the portal vein and the pulmonary vein and especially in the presence of patent portacaval anastomosis seen at postmortem examination. In Case 23 the arterial O_2 saturation and tension remained essentially unchanged after operation, which suggests that in this particular patient portacaval anastomosis did not significantly alter the degree of anoxemia. In Case 26 the presence of esophageal varices and marked portal hypertension was not associated with hypoxemia or venoarterial admixture.

The second possible site of venoarterial admixture is in the lungs and occurs in the communicating channels between the pulmonary arterioles and venules. These anastomotic channels that occur in normal lungs[22,23] become patent under the influence of various stimuli.[24] In juvenile cirrhosis these channels were demonstrated at necropsy[4] and were thought to be functioning in the adult type of cirrhosis of the liver[4,15] but were denied by others.[1,25]

In normal individuals exercise is known to reduce both the splanchnic blood flow and volume[26] while simultaneously increasing the total cardiac output (i.e., the pulmonary blood flow). Similar changes in cardiac output were described in the cirrhotic patient during exercise.[27] In these patients, if presumably *only* a porto-pulmonary shunt existed, one would expect either a decrease or no change in the A-a gradient (or degree of venoarterial admixture) on the breathing of 100 per cent oxygen during exercise, but no increase in this gradient should develop since it is inconceivable that an increase in splanchnic flow occurs. On the other hand if pulmonary arteriovenous shunts were present and admixture occurred at these sites, exercise would be expected to further

increase the A-a gradient consequent to an increase in pulmonary blood flow. In 11 patients (Table II) an increase greater than 40 mm. Hg in this A-a gradient was observed whereas in the control group 36 mm. Hg was the highest level observed. It would be safe to conclude that pulmonary venoarterial shunting exists in these patients. In Case 23, in the presence of a portacaval anastomosis, exercise resulted in a marked increase in the A-a gradient; such an increase in venoarterial admixture could only be in the lungs. In the other 9 patients the normal postexercise increase in the A-a gradient might have been due to an inadequate exercise, since many of these patients had moderate to marked ascites (Table II), or to their inability to increase their cardiac output.

Conclusion

A moderate degree of peripheral arterial desaturation is usually seen in patients with Laennec's cirrhosis. An increase in the A-a gradient during the breathing of 100 per cent oxygen and the decrease in this gradient during the breathing of 15 per cent oxygen pointed to the presence of venoarterial admixture.

A 2 minute leg exercise increased the observed A-a gradient during the breathing of 100 per cent O_2 in 11 of 20 patients, and therefore caused an increase in the magnitude of venoarterial admixture. Since splanchnic blood flow either decreases or does not change, and pulmonary blood flow increases with exercise, this increase in the magnitude of the venoarterial admixture most probably occurs in the lungs.

In 3 patients with patent portacaval anastomosis the venoarterial admixture was not obliterated and approximated theoretically the total splanchnic blood flow. In 1 patient exercise increased further the magnitude of the venoarterial admixture.

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Heart sounds and murmurs in pregnancy

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Obstetric patients are often referred for cardiological opinion because of the development during pregnancy of heart sounds and murmurs which give the impression of organic heart disease.[1] Since most cardiologists have seen diagnostic errors made in this way the present study was undertaken in order to clarify the auscultatory changes which take place in pregnancy

Material and methods

The observations were made on 50 normal primigravidas attending the Ante-Natal Clinic of the Royal Hobart Hospital Each was examined clinically every month from the time of her first attendance and when possible was followed for 1 month post partum Phonocardiograms were obtained at varying intervals on a four channel photographic recorder

Results

First heart sound † Clinical observation showed that the first heart sound changed during pregnancy the most obvious change being an increased loudness of both components which occurred at from 12 to 20 weeks of gestation. It remained loud up to about the thirty-second week, and after this there was, in a few cases, a slight diminution in intensity[2] In all cases the sound returned to normal during the second to the fourth week postpartum

The second change which was observed was the development of exaggerated splitting of the first sound This occurred at about the same time as the increase in intensity and had usually disappeared by the fourth week after delivery

The exaggerated split was at first thought to be a normal first sound followed by an early pulmonary ejection sound but analysis of the clinical observations and of the phonocardiograms showed the additional sound to have the following characteristics It was audible in the pulmonary area down the left sternal edge, and out to the apex, but was maximal in the third to the fifth left intercostal spaces close to the sternum. It consisted of both high frequency and low frequency vibrations and it neither disappeared nor diminished on inspiration The additional sound followed the beginning of the first heart sound by an interval of some 30 to 40 msec. On the basis of these findings, a pulmonary or aortic ejection sound was improbable, and the most likely explanation was that the extra sound was due to exaggerated splitting of the first heart sound In that case the first element should be caused by mitral closure and the second element by tricuspid closure.[3] In confirma

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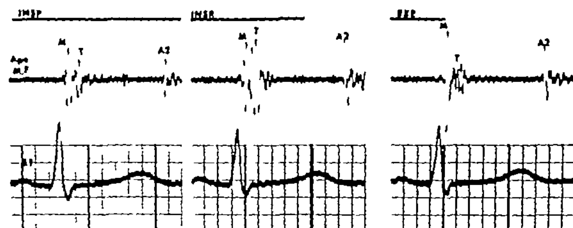


Fig. 1. The tricuspid element of the first sound (T) increases in amplitude with inspiration and diminishes on expiration. The mitral element (M) is larger just after the end of expiration.

tion of this it has been possible to show phase differences in the behavior of the two elements during respiration.[6] Fig. 1 demonstrates that the second or tricuspid element increased in amplitude on inspiration and decreased on expiration in the manner of a "right-sided" event, whereas the first or mitral element increased in amplitude on expiration in the way expected of a "left-sided" event.

In addition to the increase in intensity of the first sound there was some widening of the interval between the two elements of the split. This widening was only slight but analysis of those cases classified clinically as having an exaggerated split showed an interval of 30 to 45 msec. between the two elements. Analysis of those classified by auscultation as having no split or a normal split showed the interval to be 25 msec. or less. Of the 50 patients examined, 44 (88 per cent) showed an exaggerated split of the first sound during pregnancy.

In an attempt to find an explanation for the increased time interval between mitral and tricuspid closure, we made additional measurements on the phonocardiograms.

It was found that if the Q-1 interval were measured at a time when the split was obvious, and compared with the Q-1 interval 1 month post partum in the same patient when the split was no longer obvious, the Q-1 interval was shorter in pregnancy when the split was obvious and longer post partum when the split had gone. Table I shows these measurements made in 12 patients in whom the appropriate phonocardiograms were available. In fact, both the tricuspid and the mitral elements move toward the Q wave, but the mitral element moves more than the tricuspid, thus increasing the time interval of the split. Figs. 2 and 3 show that early closure of the mitral valve is the main feature.

Table I. Q-1 intervals measured during pregnancy and 1 month post partum showing the shorter Q-1 interval in pregnancy due to early closure of the mitral valve

Case	Q—1 (msec.) Pregnancy	Q—1 (msec.) Post partum
1	55	60
2	40	50
3	50	55
6.	45	55
8	60	70
9	45	60
10	50	60
12	33	70
13	50	60
20.	50	55
25	60	65
48.	45	60

Second heart sound. In spite of the fact that there are differences in the time intervals of mitral and tricuspid valve closure in pregnancy as compared with the nonpregnant state, no definite changes in the

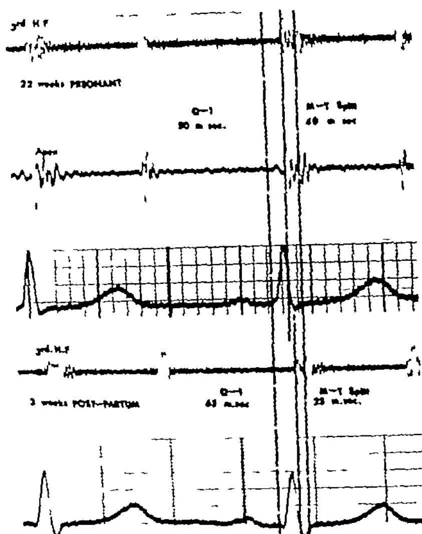


Fig. 2. Composite phonocardiogram. Upper tracing at 22 weeks of gestation; lower tracing from the same patient 3 weeks post partum. Shows the widely split first sound (*M-T split*) and the short Q-1 interval in pregnancy compared with the normal split and Q-1 post partum. (*3rd H.F.*: Third left intercostal space, high frequency.)

behavior of the aortic and pulmonary elements of the second sound could be demonstrated during the first 30 weeks of pregnancy. After this period, however, there is a tendency for the interval between the aortic and pulmonary elements of the second sound to vary less than normal with respiration. This seems to be related to lack of good diaphragmatic movement and is associated with the splinting effect of the large uterus.

Third heart sound. Although it is not uncommon to hear a soft third heart sound in normal nonpregnant young women, in pregnancy the third sound becomes loud and easily heard. This usually takes place by the twentieth week, and it is at its loudest by about 30 weeks. In some patients the intensity diminishes somewhat 2 to 3 weeks before delivery, whereas in the majority the third sound disappears or greatly diminishes within 8 days after delivery. Forty-two (84 per cent) of the 50 patients developed a loud third sound, and of these 42, 27 (64 per cent) developed the loud sound before the twentieth week.

Fourth heart sound. In 8 patients (16 per cent) a fourth sound was identified on the phonocardiogram during early pregnancy (15 to 22 weeks). In only 2 of these was the sound detected on auscultation. In every case the sound was best seen just

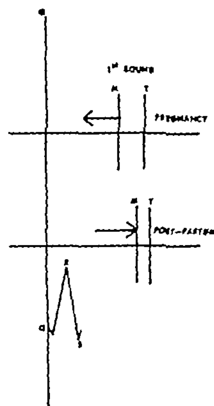


Fig. 3. Diagrammatic representation of the change in the first heart sound. M, Mitral element. T, Tricuspid element.

after the beginning of expiration suggesting that it was a phenomenon of the left side and in all cases it had disappeared by the time of delivery.

Cardiac murmurs

SYSTOLIC MURMURS. Forty-eight of the 50 patients (96 per cent) developed a systolic murmur during pregnancy. It was Grade 1 (of 4) in 8 patients (16 per cent) and Grade 2 (of 4) in 40 patients (80 per cent). *In 2 patients no systolic murmur* developed. These murmurs were of the ejection type (Fig. 4) in 46 patients and 2 patients showed what appeared to be a "pansystolic" murmur.

These two pansystolic murmurs were, more probably, long-lasting ejection murmurs, the early phases of the murmur being obscured by the transients of the loud and widely split first sound. That the murmur extended through systole as far as the aortic element of the second sound is quite possible in the case of an ejection murmur arising in the pulmonary artery.

Analysis of the phonocardiograms showed that 30 patients had early systolic ejection murmurs, 16 patients had mid-systolic ejection murmurs and no late systolic murmurs were identified.[6] Eighty-five per cent of these systolic murmurs were best heard down the left sternal edge from the second to the fifth ribs, but all could be heard quite widely over the precordium. In 7 patients the murmur was best heard in the aortic area and in 1 patient a pansystolic murmur was best heard at the apex. None of the murmurs was well conducted into the left axilla.

Effect of Respiration. Of the 48 systolic murmurs 21 were intensified on inspiration which suggests that they were right-sided murmurs probably originating in the pulmonary artery.[7] Sixteen were intensified on expiration which suggests that they were possibly left-sided in origin. Among the latter were the 7 cases in which the murmur was best heard in the aortic area, suggesting that these murmurs may have arisen in the aorta itself. In 11 pa-

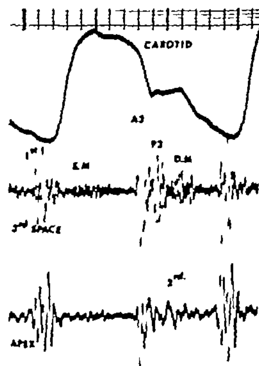


Fig. 4. Phonocardiogram showing the split first sound, mid-systolic ejection murmur (S.M.), diastolic "flow" murmur (D.M.), and loud third sound (3rd.) (Case 16.)

tients there was no change in the murmur with respiration.

Disappearance. The majority of the systolic murmurs disappeared very shortly after delivery. Of the 33 patients in whom the post-partum data on this point are complete, 22 (66 per cent) had lost the murmur by the eighth day post partum. Of the other 11 patients, 5 required 4 weeks to lose their murmurs and 6 had murmurs which were probably permanent and may have been present before pregnancy, and even these diminished in intensity within 1 week after delivery.

Of the 33 patients mentioned above, 25 had early systolic ejection murmurs; in 16 of these the murmur had disappeared by the eighth day post partum (64 per cent). Seven patients had mid-systolic ejection murmurs; in 3 of these the murmur was gone by the eighth day post partum. One of the pansystolic murmurs had gone by the first day post partum.

Audio Frequency of Murmurs. The frequency calculated from the phonocardiograms varied from about 160 to 300 c.p.s. and no particular pattern was found to emerge from a study of the murmurs from this point of view.

DIASTOLIC MURMURS. In 9 patients, a soft, medium- to high-pitched diastolic murmur occurred, often transiently; it was best heard down the left sternal edge and had a resemblance to the early diastolic murmur of pulmonary or aortic regurgitation. Study of the phonocardiograms, however, makes it doubtful whether these murmurs really were the murmurs of incompetence of the semilunar valves, and the possibility that pulmonary or aortic regurgitation develops in normal pregnancy seems to be unlikely. It is more probable that the murmur was a tricuspid "flow" murmur because it did not begin immediately after the second sound and was maximal at about the time that the third sound was heard (Fig. 4). In 2 cases there was clear evidence of an increase in intensity of these murmurs on inspiration similar to that sometimes seen in the tricuspid "flow" murmur of an atrial septal defect.[8]

The cervical venous hum is a continuous murmur that is frequently heard in children. It is less frequently heard in adults, and only occasionally over the precordium, but pregnancy is said to increase its incidence.[9] We did not encounter an example of the precordial venous hum in our series, but our technique of recording the carotid pulse on the phonocardiogram by means of an inflatable band around the neck causes a degree of cervical venous occlusion which is known to obliterate this murmur.

Murmurs originating in breast vessels. These murmurs were of two types: systolic (2 cases) and continuous (5 cases). In every case the murmur could be modified by pressure with the chest piece of the stethoscope, and in all but one case could be obliterated with firm pressure with the stethoscope or with the fingers. The most common site for these murmurs was in the right or left second intercostal space about 1 or 2 cm. from the sternal edge.

General examination throughout pregnancy showed that sharp, jerky pulses developed at between 12 and 15 weeks of gestation and lasted until about a week after delivery, in a fashion similar to the systolic murmur and the third heart sound. The pulses, which gave the impression clinically of a high pulse pressure, were not in fact associated with much of a change in the blood pressure. The jugular venous pressure rose slightly from about the twentieth week, and the venous pulse in the neck was more easily seen than usually. The right and left ventricles became easily palpable at the same time and remained so until [illegible] ment of the breasts.

Fetal death (Case 35). This patient was first seen when she was 12 weeks pregnant. She was found to have an accentuated split first sound and a grade 1 early systolic murmur. She was seen again 4 weeks later when the split was still present but the murmur had disappeared. This was the only patient who lost a systolic murmur she had once developed, and 2 days after she had been seen by us she lost the baby (at about 15 weeks). The clinical history and the condition of fetus and placenta suggested fetal death 3 days before her last examination by us, and the disappearance of the murmur therefore was probably related to fetal death.

Discussion

It is commonly stated that the [illegible] in heart sounds and murmurs

nancy are due to the effect of increased cardiac output causing an increased flow of blood through the heart valves and giving rise to turbulence. Increased plasma volume is regarded as a contributory factor.[3]

Studies on cardiac output carried out by Adams[16] showed that the cardiac output in pregnancy rose to a maximum of some 32 per cent over the nonpregnant levels at 28 weeks of gestation. Thereafter, the cardiac output decreased, reaching the nonpregnant level at approximately 38 to 40 weeks. Immediately after delivery there was another rise in output of almost 30 per cent, and normal levels were reached again in about 2 weeks. Bader and associates[11] in their catheterization studies, found that the cardiac index was raised to its maximum between the twenty-fifth and twenty-seventh weeks, and that it fell to normal prior to term. They did not continue their observations into the puerperium.

The changes in heart sounds and murmurs described in this paper started at the end of the first trimester, as did the changes in cardiac output, but the murmurs and the loud third sound continued with little alteration until about 1 week post partum. According to Adams[16] and Bader and associates[11] during the last 10 to 12 weeks of pregnancy the cardiac output is falling and may be at the pre-pregnancy level by the thirty-fifth week. The murmurs, however, were still present, and only a few cases showed a slight lessening of intensity during the last few weeks. It seems, therefore, that the behavior of the auscultatory changes does not correlate well with the alterations which take place in cardiac output.

It has been shown that the blood volume rises from the twelfth week of pregnancy to a peak at about 36 weeks, and that the level then remains unaltered until delivery.[18,23] In the early puerperium the blood volume declines sharply but not quite to normal.[18,24] It appears, therefore, that the time intervals of the changes in sounds and murmurs follow more closely the alterations in blood volume than the variations in cardiac output.

It is not known what changes take place in the viscosity of the blood during pregnancy, nor is it known what effect hormonal influences may have on the walls of large vessels, such as the aorta and pulmonary artery, but it is possible that both of these factors may alter. McDonald[14] suggests that vibration of the walls of the heart and vessels is the predominant feature in the production of heart sounds and murmurs, whereas turbulent flow in the aorta, for example, may be relatively silent.

The widely split first sound with early mitral closure is also difficult to explain because there are so few available data on hemodynamic events on the left side in pregnancy. Bader and associates[11] showed that there were changes in the end-diastolic pressure in the right ventricle in pregnancy, but whether there are similar changes on the left side is not known. Whether there is more rapid myocardial contraction due to sympathetic or other influences in pregnancy is also a factor to be considered, but again this is at present far from clear.

It seems, therefore, that a number of factors may be operating in the production of altered sounds and murmurs in pregnancy, and that changes in cardiac output and blood volume do not alone offer a satisfactory explanation.

There is controversy concerning the origin of breast murmurs in pregnancy. Tabatznik and associates[16] suggested that they were all arterial in origin, and that the junction of internal mammary and intercostal systems was the most likely point of formation. Hurst and associates[17] considered that the systolic murmurs were arterial, whereas the continuous murmurs were venous in origin. In our small series, we had no case in which the murmur was obliterated by light pressure on the surrounding breast tissue, and one case in which even firm pressure would not obliterate the murmur, although it was in the usual position and disappeared when lactation ceased. The continuous murmurs that we encountered showed systolic accentuation, which fact is more in favor of the arterial hypothesis than the "venous hum" theory.

Summary

Fifty primigravidas were examined monthly through pregnancy, and phonocardiograms were taken. During preg

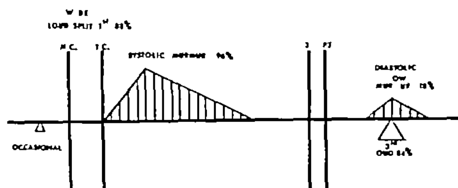


Fig 5 Summarization of the findings on auscultation of the heart in pregnancy. *M C* Mitral closure. *T C* Tricuspid closure. *A* and *P₂* Aortic and pulmonary elements of the second sound.

nancy a loud widely split first sound due to early closure of the mitral valve developed in 88 per cent. No changes in the second sound occurred other than poor movement of the two elements in late pregnancy. A loud third sound developed in 84 per cent. An occasional fourth sound was recorded (16 per cent). Ninety two per cent of the patients developed a systolic murmur of the ejection type. In 9 cases an "early" diastolic murmur developed; this murmur was thought to be a flow murmur from the atrioventricular valve. These findings are summarized in Fig 5.

Systolic murmurs (4 per cent) and continuous murmurs (10 per cent) arising in breast vasculature were also found.

The changes in heart sounds and murmurs started between 12 and 20 weeks of gestation and mostly disappeared about a week after delivery. These time intervals do not correlate well with reported changes in cardiac output, but fit better with established alterations in blood volume. It is suggested that variations in blood viscosity and in the physical state of the walls of the great vessels may play a part in the formation of murmurs in pregnancy.

Our thanks are due to the Honorary Obstetricians of the Royal Hobart Hospital for permission to study their cases.

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Endocardial fibroelastosis in American Negro children: A distinct entity?

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Until recently, the diagnosis of endocardial fibroelastosis (EFE) was considered to be possible only at the autopsy table.[1] At present, many authors consider that the diagnosis may be made with a high degree of accuracy on clinical evidence alone.[2-4] From our experience with this entity, we have established certain criteria for antemortem diagnosis (Table I) and think that a diagnosis of EFE is approachable clinically and in the catheterization laboratory.

On the basis of these criteria, this diagnosis has been made in 21 patients seen at the University of Florida Teaching Hospital. Three additional children (Cases 4, 6, and 11) who died suddenly before a definitive diagnosis could be established are also included in this study. In contrast to both our general and cardiac pediatric admissions, 75 per cent of which were white children, 18 (75 per cent) of these children were Negroes ($p < 0.05$). Our pediatric patients, with the exception of local emergency cases, are referred by physicians throughout the state. Furthermore, analysis by race revealed that these Negro children had a later onset of symptoms and a higher incidence of iron-deficiency anemia. In addition, there was suggestive evidence of a higher incidence of prematurity and a more favorable prognosis in the Negro children. These differences suggest that in our geographical area there may be a different etiology for endocardial fibroelastosis or a different expression of the same disease occurring in Negro children.

Materials and methods

This report concerns itself with 24 children in whom endocardial fibroelastosis with or without demonstrable mitral insufficiency was diagnosed by clinical and/or pathologic criteria (Tables II and III). In no case was there a known associated cardiac anomaly. All but 4 of these children were seen by at least one of the authors. Routine clinical studies, including chest x-ray films (19 cases), 14-lead electrocardiograms (21 cases), and vectorcardiograms (17 cases), were available for review. On application of the mumps antigen skin test an area of erythema greater than 10 mm. was considered to be a positive reaction. Right and/or left heart catheterization was performed in 16 patients and selective right and/or left

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Table I. Criteria for antemortem diagnosis

Clinical	*Roentgenograms*	*Electrocardiogram*	*Angiocardiography*	*Catheterization*
1. Congestive heart failure	1. Marked cardiomegaly especially of left ventricle and left atrium	1. Left ventricular hypertrophy with strain pattern	1. Large left ventricle and left atrium	1. Various degrees of left heart failure
2. Insignificant murmurs or murmur of mitral insufficiency	2. Pulmonary venous congestion may be apparent	2. Left atrial enlargement	2. Mitral insufficiency may be evident	2. Elevated pulmonary arterial pressure secondary to 1
3. No clinical or laboratory findings of rheumatic carditis, glycogen storage disease, or myocarditis		3. Biventricular hypertrophy in chronic cases	3. Increase in left ventricular wall thickness	3. No intracardiac or extracardiac shunt or semilunar valve stenosis
		4. No evidence of anterolateral myocardial infarction	4. Relatively little change in left ventricular size during systole and diastole in most cases	4. Normal systemic arterial pressures
			5. Normal origin of coronary arteries	5. Decreased left ventricular dp/dt*
			6. No aortic stenosis, ductus, or coarctation	

*dp/dt First derivative of pressure pulse.

Table II. General characteristics of white children with endocardial fibroelastosis

Case	*Onset of CHF (mo.)*	*Sex*	*Hgb*	*Birth weight (Gm.)*	*Mumps skin test*	*Follow-up*	*Diagnosis*
1	½	F	15.7	2,500	—	Died 10 wk.	CC, Ang, N
2	1	F	12.2	3,350	—	Died 6 wk.	N
3	1½	F	11.9	3,950	+	Living 29 mo. on digitalis	CC, Ang
4	2½	F	—	2,840	—	Died 11 wk.	N
5	5	M	10.3	4,180	0	Living 35 mo. on digitalis	CC, Ang
6	10	M	7.0	2,930	—	Died 10 mo.	N

—Not done. + Positive. 0 Negative. CC Cardiac catheterization. Ang Angiocardiography. N Necropsy. CHF Congestive heart failure.

heart angiocardiography was performed in all but 1 of the 16 patients. Forward venous angiograms were obtained in 2 additional patients. The size of the left ventricular cavity and the thickness of the left ventricular wall were measured by visual manual analysis using biplane 12-by 12 angiographic films in 2 patients, and by viewing cineangiograms set to equal the cardiac silhouette of standard plain x-ray films in 13 patients.

Eight patients were studied at post mortem examination. In 5 patients the clinical diagnosis of endocardial fibroelastosis was confirmed. The other 3 patients died suddenly before a clinical diagnosis was made. In 4 of the 8 patients there was evidence of shortening an

Table III General characteristics of Negro children with endocardial fibroelastosis

Case	Onset of CHF (mo.)	Sex	Hgb	Birth weight (Gm.)	Mumps skin test	Follow-up	Diagnosis
7	1½	M	8.1	2 500	0	Died 6 mo.	CC Ang no N
8	3	F	8.6	3 610	+	Living 39 mo. on digitalis	CC Ang
9	3	M	12.2	3 650	0	Living and asymptomatic 60 mo. off digitalis	CC Ang
10	6	F	—	1 760	0	Died 19 mo.	CC Ang N
11	7	M	6.8	3 180	—	Died 23 mo.	N
12	7½	M	8.9	3 060		Died 14 mo.	Ang no N
13	10	F	10.8	3 320	—	Died 15 mo.	N
14	12	F	7.3	2 680	—	Living 59 mo. on digitalis	Ang
15	12	F	7.0	3 200	0	Living 21 mo. on digitalis	CC Ang
16	13	F	5.7	2 770	—	Died 15 mo.	N
17	17	M	9.1	1 450	0	Living 35 mo. on digitalis	CC Ang
18	23	M	8.0	Full term	0	Living and asymptomatic 56 mo. off digitalis	CC
19	24	M	8.4	3 180	0	Living and asymptomatic 76 mo., on digitalis	CC
20	30	F	11.3	1 820	+	Living 51 mo. on digitalis	CC, Ang
21	28	F	—	3 640	0	Living 42 mo. on digitalis	CC Ang
22	30	M	6.5	1 900	+	Living and asymptomatic 55 mo. off digitalis	CC Ang
23	40	M	11.4	2 950	—	Living and asymptomatic 98 mo. off digitalis	CC Ang
24	61	M	12.1	4 100	0	Living 71 mo., on digitalis	CC Ang

Previous iron therapy for anemia
— Not done + Positive 0 Negative CHF Congestive heart failure CC Cardiac catheterization Ang Angiocardiography N Necropsy

thickening of the mitral valve leaflets and chordae tendineae which made the valve structurally insufficient

Results

The hemoglobin levels found in the white children were within normal limits for age except in Case 6. In contrast, 11 of the 16 recorded hemoglobin values in the Negro children at the time of admission were greater than 2 standard deviations below normal means (Fig. 1). In addition, 4 of the Negro children had been treated for iron-deficiency anemia prior to admission. In a control study utilizing 116 consecutive Negro patients, 2 months to 5 years old (mean age of 17 months) without hematologic or cardiovascular disease admitted to the pediatric ward, 50 per cent were found to fall 2 standard deviations below the normal compared to 70 per cent of the Negro children with EFE ($t = 2.4$, $p < 0.01$). None of the Negro children had clinical or laboratory evidence of sickle cell anemia.

Another difference was in the age of onset of congestive heart failure (Fig. 2). The white children had an average age of 3 months (range of 2 weeks to 10 months) at the onset of heart failure. In contrast, the Negro children had an average age of 18 months (range of 6 weeks to 5 years) ($t = 2.3$, $p < 0.01$) at the onset of heart failure. The average age at the onset of heart failure in 6 Negro children who subsequently died was 6½ months (range of 1½ to 13 months).

Among the white children, none was premature by birth weight. In contrast, 4 of the 17 (23 per cent) known birth weights of the Negro children were less than 2,000 grams (Fig. 3). In a control study of 116 consecutive admissions to the pediatric ward of Negro children without cardiovascular disease, 10 (9 per cent) had a birth weight of less than 2,000 grams. The number of Negro cases of EFE compared to the control was too small to be statistically significant at the 5 per cent level ($t = 1.0$) and therefore represents only a suggestive difference on a statistical basis.

Finally, the prognosis may appear to be more grave for white children since 4 of these 6 children have died. Both survivors have residual mitral valvular in-

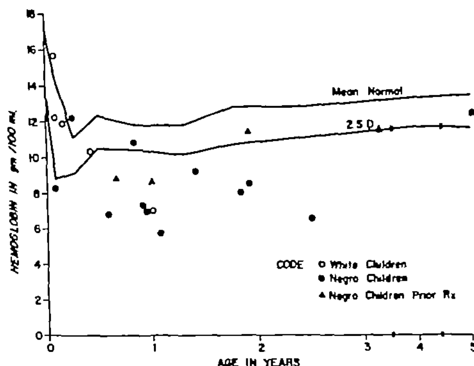


Fig. 1. A comparison of hemoglobin values in white and Negro children with endocardial fibroelastosis. Means and standard deviations for age are those quoted by Holt and associates.

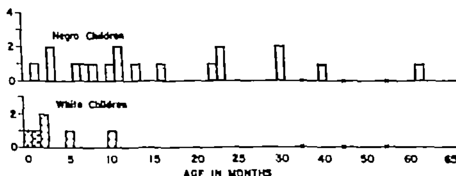


Fig. 2. A comparison of the age of onset of congestive heart failure in white and Negro children with endocardial fibroelastosis.

volvement and remain in borderline cardiac compensation. Six of the 18 Negro children have died. Four of the 12 living Negro children however are asymptomatic and no longer require digitalis. Our average follow up period for survivors in both groups is now 30 months, with a range of 9 months to 5½ years. The number of cases in both groups is too small to make a statistically significant difference.

Other clinical features. Because the physical findings in the two races were entirely comparable, with the exception of the above-stated differences, the remaining data will be discussed as one group. One half of the patients were at the twenty fifth percentile or below for weight and height and 30 per cent of this half fell below the third percentile. Only Case 6 presented with a picture of malnutrition dehydration and acidosis. Multiple con-

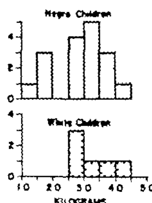


Fig. 3. A comparison of birth weights of white and Negro children with endocardial fibroelastosis.

genital anomalies with mental retardation were associated findings in Cases 5 and 17.

The major presenting complaints are listed in Table IV. Tachypnea and peripheral and generalized edema alone or in combination were found in 17 cases (70 per cent). Twelve of the children had no cardiac murmurs. However, mitral insufficiency was revealed by cardiac catheterization or necropsy in 5 of these children. Seven children had Grade 1-2/6 systolic murmurs at the lower left sternal border or apex which were not typical of mitral insufficiency. Three of these patients were found to have mitral insufficiency at the time of cardiac catheterization. Five patients with Grade 3 or 4/6 apical

Table IV. Major initial presenting complaints

Complaint	*Number of cases*
Tachypnea with facial and peripheral edema	11
Tachypnea	4
Generalized edema	2
Generalized edema and hematuria	2
Upper respiratory infection	2
Other—Enlarged fontanelle, dehydration, aseptic meningitis	3
Total	24

systolic murmurs and apical diastolic flow murmurs had mitral insufficiency that was confirmed by cardiac catheterization or necropsy.

On the basis of the thoracic roentgenograms available for review, 19 patients had evidence of cardiomegaly at the initial cardiac evaluation. Utilization of the left anterior oblique and lateral views with barium in the esophagus revealed that a combination of left ventricular and left atrial enlargement was present in 18 of the 19 patients. Case 17 had cardiomegaly but without distinct chamber enlargement. Pulmonary venous congestion was suggested by the roentgenograms of 9 patients. Patchy areas of pneumonitis were present in 3 additional patients at the time of the initial examination.

The initial electrocardiogram in 19 of 21 patients (90 per cent) showed left ventricular systolic overload.[6] Of the other 2 patients, one had biventricular hypertrophy and one had right ventricular hypertrophy. The latter, Case 17, subsequently developed a biventricular hypertrophy pattern. Catheterization revealed that he had a large left ventricle and mitral insufficiency. In addition, signs of left atrial enlargement were encountered in 11 of the 19 (58 per cent) patients with left ventricular hypertrophy. No patient showed a pattern of anterolateral myocardial infarction.[7]

Maternal and prenatal history. The average age of the mothers of this whole group of patients was 25 years. Neither parity nor a history of excessive miscarriages was significant. In all but 3 cases, the mother's health prior to pregnancy was stated to be good. One mother had chronic systemic hypertension, another had chronic iron deficiency anemia, and the third had pulmonary tuberculosis. The majority of the pregnancies were uncomplicated. Relatively common complications of pregnancy, such as anemia, pyelonephritis, and peripheral edema, were present in 5 cases.

In addition, febrile illnesses occurred in early pregnancy in 3 cases. One of these was diagnosed as lupus erythematosus with cardiac involvement. One may only speculate as to the possibility of an altered intrauterine environment in these latter cases with the febrile illnesses secondary

to a viral or some other cytopathogenic agent. A history of maternal illness, however, is not sufficiently common in cases of EFE to account for more than a small fraction of the cases.[2]

Family history. All 3 siblings of Case 17 were born prematurely. A first cousin of Case 19 has been examined by us. A tentative diagnosis of EFE was made, but this case did not satisfy the clinical criteria to be included in this study. Case 22 had a younger sibling who died elsewhere at the age of 2 years, with signs and symptoms of this disease.

Angiocardiography. Selective right and/or left ventricular angiocardiography was performed in 15 patients, and forward venous angiocardiography in 2 patients. Using the method described by Levine, Rockoff and Braunwald [9] and using normal children from our own laboratory* as controls, we found that 15 of 16 angiocardiograms showed that the left ventricular wall was thickened. The size of the left ventricular cavity was increased in 14 patients. The 2 patients who were exceptions, Cases 9 and 19, are now asymptomatic. In them the over-all heart size had decreased to normal at the time at which they were studied by angiocardiography. *In 11* instances the ratio of cavity size to wall thickness was lower than in our normal subjects.

The left atrium was visualized in 16 instances. In 14 of the 16 cases it was considered to be enlarged. Definite mitral regurgitation was noted after 7 of 10 left ventricular injections, and was suggested in 3 of 7 instances after right heart injections.

Diminished left ventricular contractility as evidenced by relatively little change between systole and diastole, as described by Linde and associates,[14] was noted in 7 of 15 instances. One patient who was thought to have normal contractility and another who was considered to have fair contractility have come to necropsy. Four of the 8 patients who were considered to have reasonably normal contractility were asymptomatic and well compensated on digitalis at the time of angiocardiography. The results of using ordinary visual-manual analysis to estimate contractility are in our experience subject to a wide range of interpretations. On the basis of our present experience, the presence of reasonably good contractility does not rule out the diagnosis of EFE.

In 13 instances, contrast visualization of the coronary arterial system was adequate to exclude the presence of an anomalous left coronary artery.

Pulmonic valvular insufficiency was an additional finding in 2 of 6 patients studied by pulmonary artery injections. No instances of aortic or tricuspid valve stenosis or insufficiency were noted in the patients studied by angiocardiography.

Discussion

All patients included in this study were considered to have EFE of the left heart, with or without demonstrable mitral insufficiency. In no case was an associated cardiac anomaly documented. In none of our patients were there clinical electrocardiographic or necropsy findings of glycogen storage disease, anomalous left coronary artery, or idiopathic myocarditis. Glycogen storage disease of the heart may be confirmed antemortem by biopsy of skeletal muscle. We have performed this study in our last 2 patients and think that it should be part of the work-up of all cases of EFE. Anomalous left coronary artery can be confirmed by retrograde aortography. Idiopathic myocarditis, in our experience can reasonably be distinguished from FFE by clinical laboratory and electrocardiographic means. We have not routinely catheterized children with idiopathic myocarditis and therefore do not have data comparable to findings in our children with EFE.

Short of necropsy confirmation some speculation must remain of a clinical diagnosis of EFE, and in its simultaneous occurrence with other disease entities, such as glycogen storage disease of the heart,[11,12] anomalous coronary artery,[13,14] and viral myocarditis.[14]

The predominance of Negro children in our study suggests either that the disease is more common in the Negro population of our geographical area or that perhaps we are dealing with a disease clinically indistinguishable from EFE, such as car

*Unpublished data.

diomyopathy in African children as was recently reported by Stein and associates.[16] Their 23 cases were similar to our Negro cases, in that clinically their patients had a later onset of symptoms (only 3 patients were symptomatic under 1 year). Other features were not similar, since their patients had a higher incidence of peripheral embolization, no mitral valve insufficiency, and a graver prognosis (14 of 23 had died). Twelve necropsy studies in this same series[16] revealed antemortem thrombi in 9 patients, and infarction of distal organs in 6 patients. The fibrous thickening of the endocardium was most prominent in the left ventricle. This thickening was diffuse in some cases, but tended to be more marked over other areas, particularly the apex of the left ventricle. In areas in which the endocardial thickening was most marked there was often necrosis and fibrosis of the subendocardial muscle fibers. This fibrosis, however, did not extend to any valves. Stein and associates[16] opined that their cases were similar to those reported in adults in South Africa and now termed cryptogenic heart disease. In contrast, our Negro children had no intracardiac thromboses at necropsy, and only 1 patient (Case 16) had distal infarction consisting of focal bilateral involvement of the kidney.

The study by Phillips and Burch[17] suggests that most of the idiopathic fibrotic myocardial and endomyocardial diseases in adults are more common in the African tribes and in the American Negro. One may thus speculate that there is a relationship between endomyocardial fibrosis in the adult American Negro and EFE in the American Negro child. However, at present there is no evidence to suggest that endomyocardial fibrosis in the adult is the end stage of unrecognized EFE in childhood.

The etiology of EFE remains obscure despite the many theories proposed.[11-26] The disease has been noted from birth to middle age and may affect more than one member of a family. A predominance of females has been reported by Kelly[4] and Moller and associates.[20] However, in general, there has been no sex or racial predilection. The disease also occurs rarely in animals.[26,27]

Recently, a viral etiology has been proposed by Fruhling and co-workers.[22] He and his associates were able to recover Coxsackie type B virus from the myocardium and other organs of 14 of 28 patients whom they described as having chronic fibroelastic myoendocarditis. Noren,[23] Sellers,[4] and Vosburgh[24] and their associates have all reported a high incidence of positive reactions to an intradermal skin test for mumps virus. This finding has led these investigators to suspect that the mumps virus or a virus with similar antigenic properties may play a role in the etiology of EFE. In addition, they believe that the skin test is a helpful adjunct in the diagnosis of the disease. The skin test has not been as specific in our experience, yielding positive results in only 4 of 14 trials (28 per cent) as compared to Vosburgh and associates' study[24] in which 67 per cent had positive reactions. Studies in human beings on the effect of mumps infection in the mother during pregnancy have yielded no cases of endocardial fibroelastosis and only a few cases of congenital cardiac malformations.[25,27]

Katz and associates[28,29] have recently published studies on experimental blockage of cardiac lymphatics in dogs, and 2 cases of impairment of cardiac lymph drainage in the human, and suggest a possible etiological role in the production of endocardial fibroelastosis.

Moller and associates[20] failed to find an instance of isolated endocardial fibroelastosis, since there was necropsy evidence of mitral insufficiency in all of their cases. Their study[20] suggests that the endocardial changes per se may not cause severe hemodynamic consequences, but that mitral insufficiency is the principal lesion.

Winter and co-workers,[33] reporting the occurrence of this disease in 2 siblings, reviewed the literature and found 9 other families with affected siblings. McKusick[34] describes EFE as occurring in 2 siblings and mentions a family in which 6 siblings had the disease. Recently, Vosburgh and associates[30] reported EFE occurring in 3 siblings. These reports, as well as our Cases 19 and 22, raise the possibility of genetic transmission.

The higher incidence of anemia later

onset of symptomatology and suggestive increased prematurity in our Negro patients with EFE, as compared to our white children with this disease suggest that hereditary environmental, and socioeconomic factors may play either an etiological or a modifying role in the expression of this clinical entity

Summary

Of 24 cases of endocardial fibroelastosis (EFE) 18 (75 per cent) were in Negro children. Our general and cardiac pediatric admissions average slightly less than 25 per cent Negro rendering this a statistically significant difference. Further analysis by race revealed that the Negro children had a later onset of symptoms and a higher incidence of iron-deficiency anemia. In addition there was suggestive evidence of a higher incidence of prematurity No further racial differences in signs, symptoms or laboratory findings were noted These differences suggest to us that EFE or a clinically indistinguishable disease is more common among the Negro children in our geographical area

Reference is made to the similarity and to the differences between our American Negro cases and the cardiomyopathy occurring in African Negro children as well as to the higher incidence of myocardial and endomyocardial fibrosis in the Negro race both in Africa and the United States

Recent speculation as to the etiology of EFE and the possible role of heredity environment, and socioeconomic factors is mentioned

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Changes in the carotid pulse which occur with age and hypertension

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There is an evident need for methods that are suitable both in large-scale studies and in clinical practice, for investigating the effects of age and disease on the human arterial system. The development of an improved transducer for the external recording of arterial pulse waves,[1] and the availability of computer techniques for the analysis of such waves prompted this investigation of the carotid pulse wave as a possible index of arterial changes associated with aging, atherosclerosis, and hypertension. The carotid artery was chosen for study because it is the most central of the readily accessible arteries. In addition to describing the changes in the carotid pulse wave which occur with aging and vascular disease, further experimental data are presented in an attempt to elucidate some of the factors determining the variations observed.

Methods and materials

Description of transducer. The transducer used for external recording of the carotid pulse has been described in detail in another communication. Essentially it consists of a metal chamber containing a diaphragm on which two strain gauges are cemented. One surface of the chamber is covered with a compliant plastic membrane, and the space between it and the diaphragm is filled with water. The plastic surface is applied to the skin over the carotid artery, and the transducer is held in place by an adjustable "c" clamp. The clamp contains an incremental ratchet which is adjusted to provide a loading pressure of approximately 20 mm. Hg to the skin over the artery. The method for determining the loading pressure has been described. The amplitude response of the transducer is flat (± 5 per cent) with no detectable phase shift to 20 cycles per second. Linearity and hysteresis are within ± 1 per cent over the working range of the instrument.

Recording and data processing. The transducer was connected to a Sanborn carrier wave preamplifier, and recordings were made on either a magnetic tape or an oscillograph recorder, or on both. Recordings were made with the subjects supine. They were instructed to hold their breath without straining for approximately 5

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seconds during which period the recordings were made. The electrocardiogram and heart sounds were recorded simultaneously. The tape recorded carotid pulse waves in some of the subjects but not in all were converted to digital form by the methods previously described.[5] Construction of an average wave for each group of subjects was accomplished by averaging every one twenty fifth ordinate over the entire cardiac cycle.

Subjects. The subjects under 25 years of age were healthy medical and college students. The patients over 25 years of age were selected from the wards of the Veterans Administration Hospital. The normal group comprised 80 subjects who exhibited no evidence of cardiovascular disease, recent loss of weight, diabetes, fever, or anemia. The 22 atherosclerotic patients had clinically documented evidence of coronary occlusion, cerebrovascular accident, or ischemic vascular disease of the lower extremities associated with atherosclerosis of the aorta or iliac arteries. The hypertensive group included 42 patients whose diastolic pressure averaged 90 mm. Hg or higher after 3 days of hospitalization. Of this number, 14 exhibited atherosclerotic complications and 28 did not.

Additional studies. In 10 patients, measurements of instantaneous blood velocity and pressure in the ascending aorta were carried out using the differential pressure gradient technique of Fry.[3] Instantaneous blood flow also was estimated when aortic angiograms were available to permit measurement of aortic cross-sectional area. The patients selected were those in whom aortic angiography or left heart catheterization was being carried out for diagnostic purposes.

In 20 additional normotensive subjects, carotid pulse waves were recorded before and after the administration of vasoactive drugs. Trimethaphan, isoproterenol, methoxamine, and angiotensin II were diluted in 5 per cent dextrose in water and administered by intravenous drip at a rate sufficient to produce a significant change in blood pressure. Methoxamine and angiotensin II were used to raise total peripheral resistance, isoproterenol to lower resistance and increase cardiac output, and trimethaphan to reduce arterial pressure, primarily by reducing cardiac output. Trimethaphan 1,000 mg. was diluted in 500 ml. of 5 per cent dextrose solution and infused at an average rate of 3 to 4 mg. per minute. Methoxamine was made up in a solution containing 0.16 mg. per milliliter and isoproterenol in a concentration of .005 mg. per milliliter. Angiotensin II was prepared by dissolving 2.5 mg. in 5 ml. of distilled water which was further diluted in 500 ml. of 5 per cent dextrose solution. Amyl nitrite was administered by inhalation. Blood pressure was measured by the auscultatory method during the administration of the drugs.

Results

The resynthesized average carotid pulse waves in the normal subjects of various ages and in the hypertensive and atherosclerotic patients revealed characteristic changes in shape (Fig. 1). The systolic portion of the carotid pulse contained two maxima. In the young subjects the first maximum was of greater magnitude than the second, whereas with increasing age the second maximum rose relative to the first and exceeded the first in the patients with hypertension and atherosclerosis. The height of the incisura relative to the first systolic maximum also rose with increasing age and vascular disease.

When the respective heights above the foot of the wave of the first and second systolic summits and the incisura were measured, the relative heights of one to another could be expressed numerically as ratios. For convenience, the first maximum was called F, the second P, and the incisura I. The means, standard deviations, and ranges of the P/F ratio and the mean I/F ratios for the groups are shown in Table I. These ratios rise with age, although there is some overlapping. There is no significant difference between the patients with atherosclerotic complications and the normal subjects who are 50 years of age and over. The hypertensive patients, particularly those with atherosclerotic complications, exhibited the highest values. The P/F and I/F ratios, therefore, appeared to be functions of both age and level of arterial pressure.

Relation of carotid pulse to aortic velocity

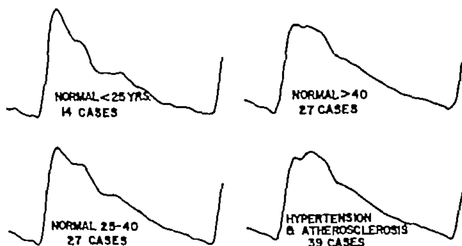


Fig. 1. Average carotid pulse waves resynthesized by averaging each twenty-fifth ordinate of the pulse cycles. The systolic portion of the wave exhibits two systolic maxima. The second maximum and the incisura increase in relation to the first maximum with increasing age and vascular disease.

Table I. Average carotid P/F and I/F ratios in normal subjects and in hypertensive and atherosclerotic patients

Group	Number	Average age (yr.)	MAP (mm. Hg)	HR (per min.)	P/F: Mean and S.D.	P/F: Range	I/F (mean)
Normal							
< 30	17	23	92	74	68 ± 13	44 – 90	35
30–49	38	40	92	74	96 ± 21	50 – 1 53	53
> 49	25	58	93	73	1 13 ± 24	52 – 1 60	64
Atherosclerosis	22	62	96	73	1 14 ± 16	96 – 1 43	58
Hypertension	28	47	135	73	1 20 ± 18	89 – 1 42	67
Hypertension and atherosclerosis	14	55	125	72	1 31 ± 23	77 – 1 78	79

and pressure and to intracarotid pressure. Instantaneous blood velocity and pressure in the ascending aorta were measured in 10 patients. Aortic angiography permitted estimation of instantaneous blood flow in a few of these patients. The carotid pulse was recorded simultaneously. In all instances in which the carotid pulse exhibited two distinct systolic maxima, the first occurred at the time of or very close to, the peak of aortic blood velocity or flow, whereas the second coincided with the peak of aortic pressure (Fig. 2). The transmission time from the aorta to the carotid was very short, varying from no detectable interval (at a recording speed of 100 mm. per second) to 12 msec. as measured from the foot of the aortic pressure wave to the foot of the carotid pulse.

The relationship between the pressure and the externally recorded pulse was further examined by recording the pressure in the carotid artery immediately beneath the external transducer in 3 patients. A Statham Model SF1 catheter tip manometer was used to record pressure. In 2 instances the carotid pressure resembled a central pressure pulse. In both of these the externally recorded pulse differed considerably from the pressure wave (Fig. 3). The external pulse rose steeply and formed the first systolic maxi-

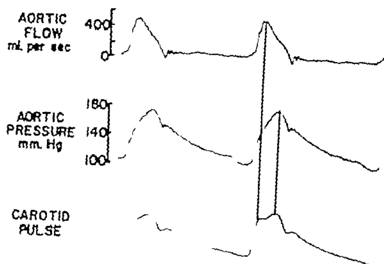


Fig. 2. Simultaneous recordings of instantaneous blood flow and pressure in the ascending aorta and the externally recorded carotid pulse. The first maximum in the carotid wave occurs nearly simultaneously with peak aortic flow whereas the second coincides with the summit of aortic pressure. Cycle length is 825 msec.

mum at the end of the anacrotic limb of the pressure wave. The external pulse then fell to form the saddle between the two maxima while the pressure wave was rising gradually to a peak. The second maximum of the carotid pulse occurred simultaneously with or near the end of the peak of the pressure wave. Both then fell to the incisura which occurred simultaneously in both the pressure and externally recorded pulse waves.

In the third patient the pressure wave resembled a peripheral pulse in that the ascending limb rose rapidly to the peak without an intervening anacrotic bend. In this case the external pulse resembled the pressure wave except that the first maximum again was exaggerated in the externally recorded pulse.

Effects of acute hemodynamic changes. The effects of increasing total peripheral resistance on the externally recorded carotid pulse was determined by intravenous administration of methoxamine or angiotensin II. Both of the agents have little or no myocardial inotropic effect in man causing vasoconstriction without change or a reduction in cardiac output accompanied by bradycardia that is reflexly induced.[4] Both methoxamine in 8 subjects and angiotensin II in 9 showed similar changes characterized by a rise in P/F and I/F ratios (Table II). A typical response to angiotensin II is shown in Fig. 4.

Total peripheral resistance was decreased in 8 subjects by inhalation of amyl nitrite. This agent produces a transient reduction in arterial pressure accompanied by an increase in cardiac output.[4] During the fall in blood pressure after inhalation of amyl nitrite the anacrotic limb of the carotid pulse became less steep rising more gradually to the F peak. The second systolic maximum and the incisura declined relative to F and the former usually disappeared at the time of the maximum hypotensive effect of the drug (Fig. 5). For this reason it was not possible to calculate a I/F ratio. The mean decrease in I/F ratio was 47 per cent (Table II).

To examine further the mechanism for the profound changes produced by amyl nitrite in the carotid pulse 3 patients were given the drug during determinations of aortic blood velocity (Fig. 5). During the control period maximum aortic pressure occurred after peak aortic blood velocity whereas after the inhalation of amyl nitrite the two peaks occurred simultaneously and the anacrotic limb of the aortic pressure disappeared. At this time the carotid pulse wave exhibited a single systolic maximum.

Trimethaphan, a ganglion blocking agent was used to lower arterial pressure without increasing cardiac output.[5] The drug was infused at a rate that produced average decreases of 25 and 29 per cent in mean

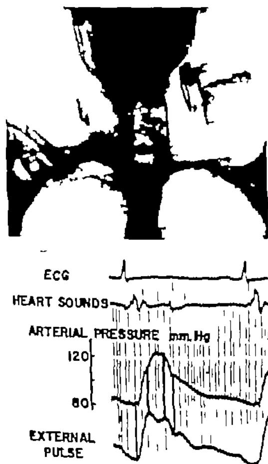


Fig 3 Simultaneous recordings (*from above downward*) of the electrocardiogram heart sounds intracarotid pressure and the externally recorded carotid pulse. Position of the transducers is shown in the roentgenogram above the pressure transducer is indicated by the arrow. Time lines are at 20-msec. intervals. See text for description of shapes of pulse waves.

arterial and pulse pressures respectively (Table II) As was the case after amyl nitrite the second maximum of the carotid pulse declined relative to the first and disappeared in 5 of the 8 subjects studied The mean decrease in I F ratios was 39 per cent.

The effect of peripheral vasodilatation plus adrenergic stimulation of the heart was determined in 6 subjects by the intravenous administration of isoproterenol The potent inotropic effect of this drug was reflected in the increase in pulse pressure which averaged 140 per cent (Table II) Diastolic pressure fell as systolic rose so that mean arterial pressure was un-changed The carotid pulse wave (Fig 6) exhibited a considerable increase in the F summit and a fall in the P maximum producing a decrease in P F ratio that averaged 35 per cent The incisura also fell relative to the F peak with the average decline in the I/F ratio being 44 per cent.

The effects of the vasoactive drugs on diastolic pressure and I F ratio are summarized in Fig 7 The mean changes are plotted to show the linear relationship between change in diastolic pressure and change in I F ratio with the various agents.

Discussion

At the present time basic hemodynamic data such as flow pressure pulse and arterial wall elasticity cannot be obtained by simple atraumatic methods. In the absence of such data indirect indices, such as externally recorded pulse waves, may provide clinically useful information. In the development of such indirect methods the transducer design should incorporate ease of application as well as accurate representation of the function to be studied. The transducer used in the present studies has proved to be practical for clinical application while providing adequate linearity and frequency response

Despite the use of an improved transducer the externally recorded carotid pulse wave is not a good facsimile of directly recorded movements of the surgically exposed carotid artery The latter both in the dog[7] and in man[8] closely parallels the shape of the recorded carotid pressure pulse By contrast the external pickup accentuated the first systolic maximum of the carotid pulse wave, as compared to the pressure pulse The reason for this discrepancy is not clear The accentuation may be due to oscillations produced by the tissues that intervene between the transducer and the carotid artery or to the static loading pressure of 20 mm Hg used to obtain the recordings. On the other hand with the same methods no gross discrepancies could be detected between the external and intra-arterial pressure pulse of the brachial artery [1] This suggests that the distortions seen in the externally recorded carotid pulse probably are the result of factors peculiar to its location The carotid artery probably is not so well tethered as the brachial artery Further-

Table II. Per cent changes in blood pressure, cycle length, and P/F and I/F ratios after vasoactive drugs

Drug	Subjects (number)	Average age (yr)	Per cent change									
			Blood pressure				Cycle length		P/F		I/F	
			Mean		Pulse							
			Av	S.D.	Av	S.D.	Av	S.D.	Av	S.D.	Av	S.D.
Methoxamine	8	39	+41	2	+42	46	+20	12	+31	16	+61	14
Angiotensin II	9	40	+42	16	+30	39	+24	22	+54	41	+51	38
Amyl nitrite	8	37	−39	6	−20	14	−18	12			−47	20
Trimethaphan	8	38	−25	7	−29	21	−13	6			−39	17
Isoproterenol	8	40	−2	11	+140	92	−21	13	−35	21	−44	15

P maximum disappeared in 4 of the 8 subjects after amyl nitrite and in 3 of 8 after trimethaphan.

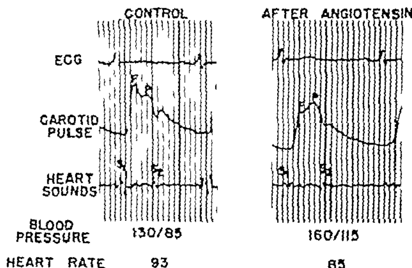


Fig. 4. Recordings of electrocardiograms, carotid pulse wave, and heart sounds before and after infusion of angiotensin II. Time lines are at 0.04-sec. intervals. See text for further details.

more it may be subjected to significant tugging along its longitudinal axis produced by the movements of the heart and aorta within the thorax during the cardiac cycle. These movements could produce longitudinal displacement of the carotid artery which would be reflected in the external pulse recording.

The assessment of an indirect index of cardiovascular functions such as the externally recorded pulse wave is largely empirical. Correlations are made between recorded changes in the pulse wave and other parameters, such as age, blood pressure, and various known cardiovascular disorders. Yet attempts should also be made to explain the observed changes in pattern in terms of hemodynamic functions. With regard to the latter, two approaches were used: one was to correlate aortic blood velocity and aortic pressure or carotid pressure in the resting state with the simultaneously recorded carotid plethysmogram, and the other was to observe changes produced in the carotid pulse by acutely induced changes

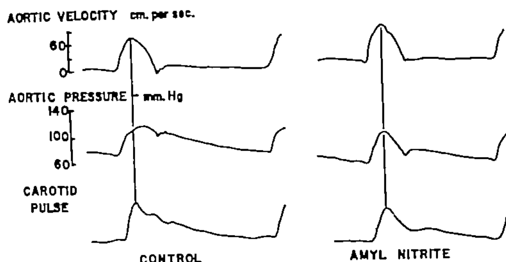


Fig 5 Recordings similar to those in Fig 2, before and after inhalation of amyl nitrite. The lines of the recordings have been strengthened with India ink.

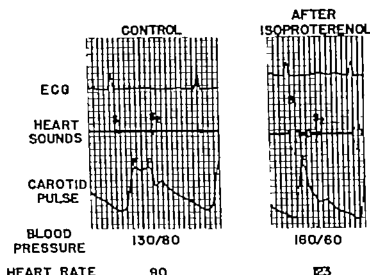


Fig 6 Recordings similar to those in Fig 4 before and after infusion of isoproterenol.

in central arterial pressure and flow

In the first of these two experimental approaches, the initial systolic maximum of the carotid pulse occurred nearly simultaneously with the peak of aortic blood velocity. This point also corresponded with the anacrotic bend of the aortic pressure pulse. Thus, the first systolic maximum of the carotid pulse occurred during the period of acceleration of the aortic-carotid blood column. The latter produces a steep pressure gradient that culminates in the anacrotic bend of the pressure pulse. In the externally recorded carotid pulse wave this event was displayed as a definite summit which was most prominent in the young patients at rest or in others after stimulation of myocardial contractility with isoproterenol.

After the anacrotic bend and during the phase of diminishing aortic blood velocity, the aortic pressure pulse usually rises to its summit. At this latter time the second systolic maximum was inscribed on the externally recorded carotid pulse. Thus the second maximum of the carotid pulse

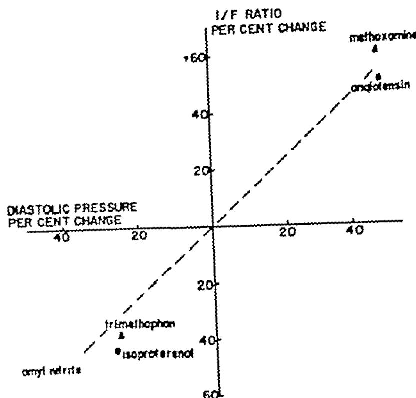


Fig 7 Plot of the mean changes in I/F ratio (*on the abscissa*) against mean changes in diastolic pressure (*on the ordinate*) produced by the various vasoactive drugs A linear relationship between I/F ratio and changes in diastolic pressure is shown

usually was associated with peak systolic aortic pressure As has been shown by Peterson[9] the late systolic rise in aortic pressure is a consequence of pulsatile flow in distensible tubes with restricted outlets When peripheral runoff is impeded the tube becomes distended late in systole, wall tension consequently increases and lateral pressure rises Increased peripheral resistance is the probable reason for the prominence of the second systolic maximum as seen in the hypertensive patients as well as in normal subjects after angiotensin or methoxamine

On the other hand Peterson found that pulsatile flow in distensible tubes with no restriction to outflow produces only the initial and not the second systolic pressure maximum The initial pressure maximum is due to inertial effects associated with acceleration of the blood Obliteration of the second systolic maximum occurred in our subjects after the inhalation of amyl nitrite This substance is known to markedly decrease peripheral vascular resistance.[3]

The increase in the second systolic maximum of the carotid pulse observed with increasing age in the normotensive subjects probably is associated with structural changes in the arterial wall Aortic distensibility decreases with age,[10] presumably because of an increase in collagen in the wall[11] Peterson[9] found that changes in the elasticity coefficients of the distensible tubes used in his model studies markedly influenced the shape of the pressure pulse If this is the case, the relative magnitude of the two systolic maxima of the carotid pulse may provide an index of central arterial distensibility provided that cardiac output and total peripheral resistance are normal

The height of the incisura relative to the foot of the wave was related directly to the magnitude of the second systolic maximum After vasoactive drugs it rose when the second maximum increased and fell when the latter decreased or disappeared This relationship probably is a consequence of the close temporal relationship between these two inflexions since the

incisura follows soon after the inscription of the second systolic summit.

The clinical and epidemiological usefulness of carotid pulse recordings will depend ultimately on the closeness of the correlation between changes in the pattern of the carotid wave and other variables, such as blood pressure, age, and cardiovascular abnormalities. With regard to the shape of the pulse wave, the observed increase in the height of the incisura and second systolic maximum relative to the first occurring with advancing age and hypertension has also been noted by other investigators.[11-13] They likewise found as in the present study that the shape of the carotid pulse was essentially the same in patients with atherosclerotic complications as in "normal" subjects of similar age. Thus, the changes in pulse observed with age probably are associated with alterations in wall structure other than those produced by atherosclerosis, but, nevertheless, result in a reduction in wall distensibility.[10-14]

To determine the closeness of the correlation between aging and changes in the carotid pulse wave, larger samples will be required. The reproducibility of pulse waves obtained on the same individuals on different days also remains to be determined. The present results are sufficiently encouraging however to warrant further investigation of the carotid pulse wave as an index of the effects of aging on the central arterial system.

Summary

The carotid pulse wave was recorded in normal subjects of various ages and in hypertensive and atherosclerotic patients, using a water filled transducer with improved performance characteristics. The feasibility of analyzing such waves by electronic data processing has been demonstrated.

The changes in the carotid pulse wave occurring with age are similar to those found in hypertension but are of lesser degree. The wave contains two systolic maxima, the first related temporally to peak aortic flow and the second to maximum aortic pressure. With increasing age or hypertension the second maximum and the incisura rise in relation to the first systolic maximum. Similar changes can be induced with agents which increase total peripheral resistance whereas opposite changes are produced by vasodilator drugs.

It is suggested that the changes observed in the carotid pulse wave are a reflection primarily of central arterial distensibility. The potential usefulness as well as the limitations of the method are discussed.

We are indebted to Hubert Pipberger, M.D., for converting the pulse tracings from analogue to digital form and for the use of programming and computer facilities.

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Experimental and laboratory reports

Fiber optics for continuous in vivo monitoring of oxygen saturation

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In recent years considerable interest has developed in the use of fiber optics catheters for the determination of oxygen saturation and dye concentration using spectrophotometry.[1-4] The general techniques that are currently being used are based on reflection oximetry methods pioneered by Zijlstra[5] and others.[7,8] It is clear that significant progress has been made in using reflection oximetry for the accurate determination of oxygen saturation in vitro[1,2] as well as in vivo through fiber optics cardiac catheters.[1-4,4] The extension of these techniques to permit the continuous monitoring of oxygen saturation over a period of several hours has been dependent on developments in fiber optics.[10,11]

The basic principles involved in the techniques used in our laboratories for the continuous monitoring of oxygen saturation are briefly these. Light from a tungsten lamp is transmitted through a portion of a fiber optics bundle which is incorporated into a cardiac catheter. This catheter is introduced into a peripheral artery or vein or directly into the heart. The afferent light is transmitted to the blood at the tip of the catheter where it is scattered by the red cells. A portion of this light is back-scattered (or reflected) and this light is picked up by two other sections of the fiber optics bundle. These efferent light intensities are the signal inputs which are detected by photomultiplier tubes and electronically processed. The ratio of the intensities of the efferent light at 805 and 660 millimicrons is then computed and recorded. This ratio is a linear function of the oxygen saturation as determined either by reflection or transmission oximetry.[1,4,4]

It is apparent that the continuous monitoring of oxygen saturation in the heart is desirable for the determination of cardiac shunts. More recently investi-

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gators and clinicians have been interested in continuously monitoring the arterial oxygen saturation of patients during surgery or postoperatively in intensive-care units. Clinical physiologists have also been interested in the recording of oxygen saturation in patients with advanced pulmonary disease, in which case a delicate balance of a number of respiratory mechanisms must be continually regulated.

This report describes experiments with fiber optics systems which have been used for the continuous monitoring of oxygen saturation on the venous side of the circulation in the heart and in peripheral arteries. The equipment is described, its in vivo and in vitro characteristics are defined, and representative records that were obtained with the equipment when blood oxygen saturation was varied are shown.

Materials and methods

The fiber optics oximeter is a spectrophotometer which measures the back-scatterd light from a dynamic specimen which is remote from the instrument. The system used in this study was developed by Optics Technology, Inc., and is described in detail elsewhere.[1,2] The basic design of the equipment is shown schematically in Fig. 1. It consists of (1) a tungsten light source, (2) a flexible catheter which contains three optical channels—the flexible fiber optics bundle that transmits light from the source to the blood stream and two flexible fiber optics bundles that return the reflected light to a pair of filter photomultiplier tube combinations, (3) an amplifier and associated electronics for each channel and (4) a recorder that computes the ratio of the two signals and prints this ratio on a continuous chart. The light source for the oximeter is chopped at 330 c.p.s., which gives the system a theoretical response time of less than 1 millisecond, and the amplifiers are tuned to this frequency with a narrow band pass.

The optical-quality catheters consist of flexible glass-coated glass fibers, 50 microns in diameter, which have an absorbing film on the outer surface of the coating glass to minimize optical cross-talk. These fibers, totaling from 20 to 120, depending on the type of catheter, are divided into three channels. Of the three, the transmitting channel contains twice as many fibers as each of the two return channels, and the fibers in all of the channels are randomly mixed at the distal end to assure good sampling of the light reflected or back

Fig. 1. Schematic and block diagram of the fiber optics oximeter and catheter for continuously monitoring oxygen saturation.

scattered by the red blood cells The light from one of the return channels passes through an 805 millimicron filter and that from the other return channel passes through a 660-millimicron filter both have a 1 per cent band pass. The light that passes through the filters is detected by photomultiplier tubes, and the output signal is amplified and fed into the recorder A computer in the recorder determines the ratio of the 805-millimicron signal to the 660-millimicron signal This ratio which

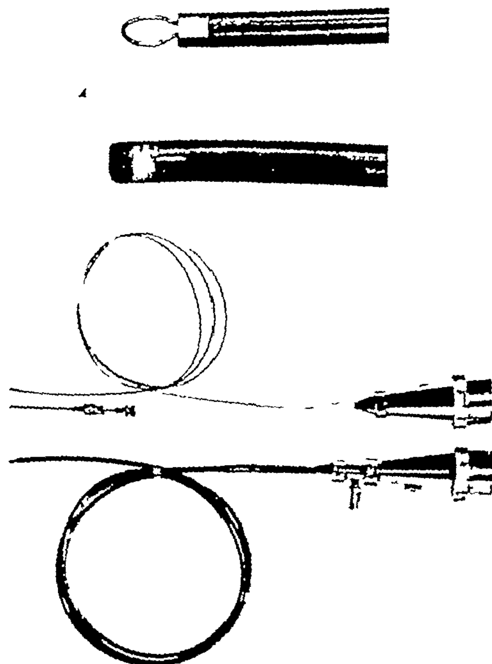


Fig 2 *A* Intracardiac catheters with shielded tips *B* Intra arterial and intravenous catheters. The small catheter can be inserted into an artery or vein through the No. 18 needle with a stylus in place.

is directly related to the oxygen saturation of the blood is then printed on a strip chart as a permanent, continuous real time record

The various types of fiber optics catheters that were used with the recording system are shown in Fig 2,*A* and *B* These catheters are of two general types, intracardiac (2,*A*) and intravascular (2 *B*) In the intracardiac catheter the distal end is shielded to keep the fiber bundle from touching the wall of the heart as it expands and contracts, inasmuch as the return light will not be back scattered from red cells should the bundle touch the wall and the oxygen saturation recorded by the oximeter will be erroneous. Two types of protected catheter tips have been used successfully One consists of a distal wire loop made of platinum-coated molybdenum which is sealed into the catheter tip The second type of intracardiac tip is formed by placing a polyethylene-covered fiber bundle within a Goodale-Lubin type catheter as shown in Fig 2,*A* The tip of the fiber bundle is placed just beyond the proximal end of the side holes so that there is a good flow of blood past the fibers while the outer catheter keeps the fibers away from the wall of the heart. The advantage of this type of catheter is that the annular space between the fiber bundle and the outer catheter provides a lumen which can be used for the recording of pressure or the withdrawal of samples of blood With this type of design it is essential that the length of the catheter be maintained precisely Therefore a Goodale-Lubin catheter of Teflon was selected rather than one of woven Dacron with which the length changes as much as 1 cm in a 125-cm catheter These intracardiac catheters are easily seen on fluoroscopy and can be maneuvered into various cardiac chambers without difficulty

The intravascular catheter on the other hand needs no protection at the distal end since it is not exposed to a strongly pulsating vessel wall One type of intravascular catheter consists of a Teflon covered fiber bundle within a No 9 French catheter as shown in Fig 2 *B* The fiber bundle extends about ¼ of an inch beyond the end of the catheter The annular space again can be used for the recording of pressure or the withdrawal of samples of blood Another type also shown in Fig 2,*B* consists of a small fiber bundle within and 0 038-inch polyethylene tube which can be inserted percutaneously into either an artery or vein through a thin walled No 18 needle A needle with a sharp stylus is used to insert this catheter into vessels After the catheter is securely in place the needle is removed Such a catheter can be left in the vessel for long term monitoring of oxygen saturation.

The fiber optics oximeter was used to determine oxygen saturation continuously in 25 dogs Before each study the equipment was calibrated by placing the tip of the catheter in sterile milk of magnesia Milk of magnesia was chosen for this purpose because it could easily be sterilized and it appeared to give a reproducible reflection of light as a white-reflection medium[*] The ratio of the light which is reflected at 805 and 660 millimicrons in milk of magnesia corresponds to an oxygen saturation of 97 per cent when compared to oxygenated blood Throughout the investigations, samples of blood were drawn at intervals, through the double lumen catheters, and the oxygen saturation was determined in vitro by reflection[*] or transmission[†] oximetry In 14 dogs the oxygen saturation of the blood was varied by ventilating the animals [illegible] mixtures with oxygen concentr[illegible] 6 8 21 and 100 per cent The [illegible] administered chloralose (75 mg [illegible] gram) and urethane (300 mg per [illegible]) to produce a moderately deep [illegible] anesthesia An endotracheal [illegible] serted and a Bennett resp[illegible] with a positive pressure [illegible] mixture. Arterial pressur[illegible] cardiac contractile force were [illegible] continuously in all of the dogs [illegible] tractile force was deter[illegible] ton Brodie strain gauge [illegible] with a Wal[illegible] onto the right ventricle [illegible] the end of each study the gauge [illegible] librated with weights, and the [illegible] pressed in grams [illegible] to give [illegible] observed deflection The position of

[*]American Optical [illegible]
[†]Beckman Model [illegible]

catheter was verified in every case by direct palpitation or fluoroscopic examination When the possibility of protein coagulation or blood clotting on the tip of the catheter was suspected the catheter was immediately removed and visually inspected In several studies fibrin coagulation was observed at the end of the fiber optic bundles, and in some cases a thin filament of a blood clot was subsequently formed Occasionally when sutures were tied very firmly around the catheters some of the fiber bundles would fracture

Results

A Correlation of oxygen saturations A correlation analysis was performed and 95 per cent confidence intervals were calculated for the oxygen saturation correlations[14] The oxygen saturations determined with fiber optics methods show close correlation with the oxygen saturations determined by conventional spectrophotometric methods (Fig 3,*A* and *B*) in samples of blood drawn simultaneously from the heart or from peripheral vessels. Most of these observations were made in the right atrium and right ventricle by intracardiac catheters (Fig 2) These catheters were maneuvered easily within the heart For samples of blood from the central veins and the right side of the heart, the correlation coefficient is 0 98 and is significant at p less than 0.01 The equation for the regression line is

$$Y = 1.056\,(X) + 20.2$$

where Y represents the ratio reading from the fiber optics catheter and X represents the oxygen saturation of samples of blood Ninety five per cent confidence intervals were calculated for the regression line and are represented by the curved broken lines in Fig 3,*A*

The correlation coefficient for samples of peripheral arterial blood is 0 97 with p less than 0.05 The equation for the regression line is

$$Y = 1.079\,(X) + 16.9$$

In this case 95 per cent confidence intervals for the regression line are not so precise as those for venous blood probably because of the smaller number of samples taken (Fig 3 *B*)

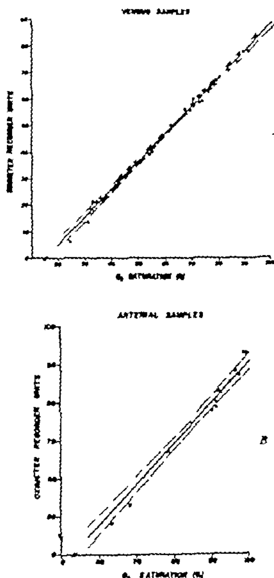


Fig 3 Ratio recordings from the fiber optics oximeter versus oxygen saturation determined by standard means on samples of blood drawn simultaneously from the venous circulation and heart (*A*) and from the artery (*B*). The solid lines represent the regression lines and the curved broken lines represent the confidence intervals for the regression lines.

B Oxygen saturation at various gas mixture concentrations When the animals were ventilated on gases with varying oxygen concentrations wide variations were observed in the oxygen saturation of blood in the venous system. In the vena cava wide fluctuations were noted with each respiratory movement These changes have been attributed by other investigators[3] to streaming of blood



Fig. 4 Typical record from a dog that was ventilated on 8 per cent oxygen. The absolute oxygen saturation scale is shown at the left, and the various events which were changed are listed in the margin. Note the rapid return of the arterial blood to 95 per cent oxygen saturation upon ventilation with 100 per cent oxygen.

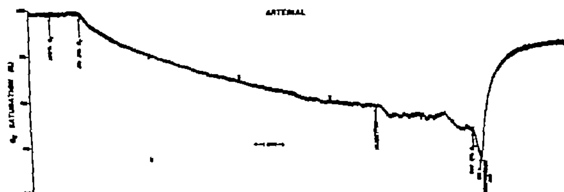


Fig. 5 Record of the continuous monitoring of arterial oxygen saturation in a dog on various gas mixtures. The initial part of the record was made on 100 per cent oxygen, followed by 8 per cent oxygen and at the end the animal was ventilated with air.

The arterial oxygen saturation was continuously monitored in 14 animals while oxygen of various concentrations was supplied to them through a Bennett respirator. A typical example of a record of the arterial oxygen saturation determined with the fiber optics system is shown in Fig. 4. It is of particular interest that the arterial oxygen saturation returned to 95 per cent values within seconds after 100 per cent oxygen was administered to the animal (Fig. 4). Arterial and venous oxygen saturation was monitored for as long as 6 hours in these animals. A 20-minute strip of record from one such study is shown in Fig. 5.

During hypoxia induced by inspiring 8 per cent oxygen, the mean arterial pressure changed only slightly from an average of 128 ± 12 to 120 ± 19 mm. Hg, the heart rate changed from an average of 140 ± 19 to 144 ± 13 per minute, and the right ventricular contractile force changed from an average of 53 to 47 grams. None of these changes is significantly different from the control observations.

C. Effects of flow and hematocrit. Since it is possible that the hematocrit of the blood and the rate of flow may affect oxygen saturation as measured by in vivo techniques, in vitro studies were performed under various conditions of blood

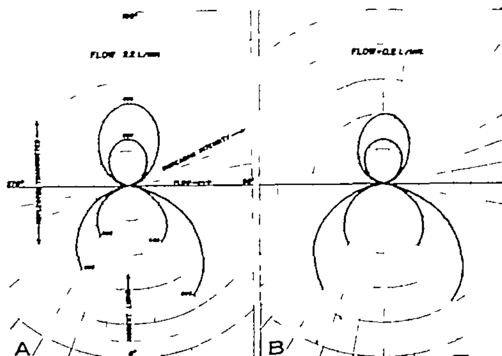


Fig 6 Polar plots of the transmission and reflection of light at 660 and 805 millimicrons when incident light was directed at right angles to a column of blood (0-180°) moving through Tygon tubing from left to right flow 270° to 90° at 2.2 L. per minute (A) and 0.2 L. per minute (B) Note only small changes in the reflection of light at these various flow rates

flow and hematocrit. Spectrogoniophotometric methods were used to measure oxygen saturation under dynamic flow conditions ranging from 200 to 2 200 ml per minute. A rotameter was used to control flow through Tygon tubing and the intensity of the light scattered by the red cells under these conditions was recorded

Studies in the laboratory demonstrate that wide changes in blood flow affect both the transmitted and the reflected light (Fig 6) However at extremely high flow rates the ratio of light reflected at 660 and 805 millimicrons is only slightly different from that at lower flow rates as shown in Fig 6 Since the changes are small with a tenfold increase in flow rate the oxygen saturation determined by in vivo techniques would be accurate for all but extreme situations in which flow rates might change by more than ten times the control values.

Changes in the reflection of light at 660 and 805 millimicrons also occur when the hematocrit is varied from 20 to 61 per cent as shown in Fig 7 These changes are small when the changes in hematocrit are small as are observed in acute experiments.

Discussion

By combining the techniques for determining oxygen saturation by reflection oximetry with fiber optics technology rapid and continuous measurement of oxygen saturation of blood in the vascular system and the heart is possible without the withdrawal of samples of blood The fiber optics system has provided results which have proved to be linearly related to oxygen saturation the system is highly stable, and it has rapid response characteristics. The agreement of oxygen saturations of blood drawn simultaneously and determined by conventional spectrophotometric techniques with those obtained with the fiber optics system is very encouraging The validity of this agreement is characterized by the correlation coefficients of 0 98 and 0 97 for venous and arterial blood respectively and the use of milk of magnesia for calibration of the equip-

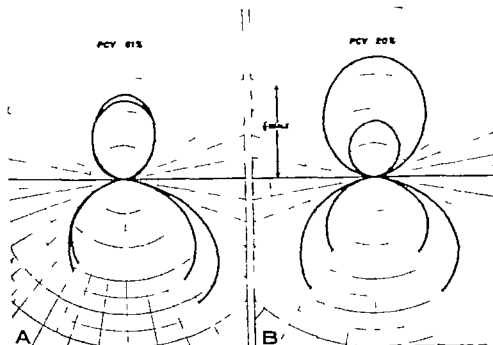


Fig 7 Polar plots of the transmission and reflection of light at 660 and 805 millimicrons when the hematocrit of 100 per cent oxygenated blood was altered from 61 per cent (A) to 20 per cent (B). Legend is same as for Fig 6. Note that in B the scale has been reduced to one fourth of the original on the transmission of light. Changes in hematocrit markedly alter the transmitted light but has a somewhat smaller effect on the reflected light (compare A and B).

ment has greatly simplified its use. The results reported are similar to those observed by several other investigators.[2-4] In addition Gamble and his associates[2] and Frommer and his associates[3] have described the use of a similar fiber optics oximeter for the detection of intracardiac shunts in patients with congenital heart disease. They have employed various cardiac catheters incorporating bundles of optic fibers to successfully demonstrate shunts immediately upon moving the catheters within cardiac chambers and without the necessity of removing samples of blood. The correlation of oxygen saturations determined by fiber optic methods with those determined by the usual methods of oximetry was extremely reliable in the hands of these investigators[2,4] and is in close agreement with the observations reported in this study.

The rapid response time of the system used by Gamble and associates[2] and Frommer and associates[3] allowed a study of changes in oxygen saturation within portions of the cardiac cycle in patients with congenital heart disease. Although no such observations were made in the present study wide and rapid changes in oxygen saturation in the vena cava and right atrium were observed with respiration probably resulting from streaming of oxygenated and unoxygenated blood. The rapid response of this instrument is also apparent from Fig 5 in which the oxygen saturation of arterial blood is shown to return to 95 per cent almost instantaneously upon ventilation with 100 per cent oxygen.

The value of this system for continuously monitoring arterial oxygen saturation has been enhanced by the development of small fiber bundles which can be introduced into an artery through a needle (Fig 2 B). When used these small catheters eliminate the need for surgical procedures on vessels, and they can be inserted into any peripheral artery or vein. Hugenholtz and associates[4] and Frommer and associates[3] have demonstrated that,

when the 660-millimicron filter in their system was replaced by one transmitting light at 905 millimicrons and the circuit was switched to calculate the ratio of light reflected at 905 to 810 millimicrons the instrument became sensitive to Cardio-Green dye Cardiac outputs determined by this method closely approximated those determined by standard densitometry[4,8] It is clear that a small catheter which could be inserted into an artery for long periods of time would permit the use of this instrument as a recording densitometer to determine cardiac output intermittently in patients who are severely ill Therefore by changing one filter in the instrument it could serve to monitor continuously the oxygen saturation and be used to determine cardiac output at desirable intervals.

The effects of changes in blood flow and hematocrit on the light reflected at 660 and 805 millimicrons and thus on the oxygen saturation recorded with this instrument may be significant when large variations in these parameters are induced However changes in flow and hematocrit within the physiologic range in acute experiments do not affect the oxygen saturation determined with this equipment The changes in reflected light produced by alterations in flow and hematocrit certainly merit further study and the possibility of measuring blood flow with these techniques is under investigation[16]

Summary

The use of reflection oximetry when combined with fiber optics allows for accurate determination and long term in vivo monitoring of oxygen saturation in peripheral vessels and in the heart. The oxygen saturations determined by fiber optics oximetry show excellent agreement with those obtained by routine spectrophotometry Studies on the effects of variation in flow and hematocrit on the oxygen saturation determined by these methods are discussed

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The significance of postmortem coronary arterial perfusion studies

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No direct measurements of individual flows in the right and left coronary arteries of the intact human heart have been reported. Although rapid progress has been made in the investigation of instantaneous coronary flow in the intact unanesthetized laboratory animal, the preponderance of information in regard to flow in the coronary arteries of man has been derived from perfusion studies performed upon human hearts obtained at autopsy. Recent postmortem investigations of the characteristics of coronary flow in human hearts have shown significant variations in the volume and distribution of flow in the individual coronary arteries.[1] The present study was undertaken to determine the alterations in individual coronary arterial flow values resulting from time-dependent postmortem changes in the human and dog heart.

Methods

Fifty-four human hearts were obtained at autopsy at periods ranging from 1½ to 12 hours after death. In all patients the primary cause of death was not attributable to heart disease. As a related study, 48 dogs were anesthetized with sodium pentobarbital (25 mg. per kilogram) and killed by rapid asphyxiation. After death had been confirmed by cessation of respiration and heart action, the dog hearts were removed from the chest either immediately or at intervals of 1 to 6 hours. Both human and dog hearts were trimmed of extraneous fat and pericardium and then weighed. The ostia of the right and left coronary arteries and that of the coronary sinus were cannulated with plastic catheters of appropriate size. The coronary arteries were connected to a perfusion apparatus as illustrated in Fig. 1. During perfusion the coronary sinus drainage was collected in a graduated cylinder.

Each heart was immersed in a constant temperature bath at 37°C. and the coronary arteries were perfused at a constant mean pressure of 100 mm. Hg with isotonic saline solution maintained at a temperature of 37°C. Individual coronary arterial flows and coronary sinus return were measured. The dog hearts were perfused either immediately after death or at intervals after removal from the dog. Each heart was perfused at only *one* of the designated times. At the conclusion of the perfusion the heart was again weighed, and the total amount of saline utilized in the perfusion was recorded. The value for coronary arterial flow was the average of three 1 minute periods of perfusion.

The coronary arterial and coronary sinus flows for the 54 human hearts and 48 dog

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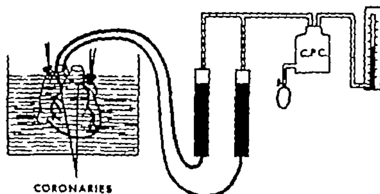


Fig. 1. Diagrammatic illustration of the method employed for perfusion of the coronary circulation. C.P.C. represents the constant pressure chamber. (See text for description of details.)

Table I. Results of postmortem perfusion studies of the coronary circulation of human and dog hearts

Time after death (hours)	*Number of hearts*	*Average heart weight (Gm.)*	*Average coronary arterial flow (c.c./100 Gm./min.)*	*Average coronary sinus flow (c.c./100 Gm./min.)*	*Average coronary sinus flow (% Coronary arterial flow)*	*Average increase in heart weight (Gm./100 c.c. perfused)*
Dog hearts						
Immediate	7	97	115	48	42	3
1	7	87	93	40	43	5
2	6	89	58	20	34	10
3	10	95	41	9	22	13
4	4	108	39	5	13	13
5	5	92	36	4	11	14
6	6	94	31	2	6	15
Human hearts						
1½	1	312	96	32	42	5
2-3	2	317	73	22	30	9
3-4	6	282	62	14	23	12
4-5	7	306	47	9	19	15
5-6	7	310	40	4	10	17
6-12	31	417	30	2	6	21

hearts, and the changes in heart weight which accompanied the perfusion are summarized in Table I.

Results

In both the human and dog hearts the volume of flow that could be perfused through the coronary vascular bed decreased as the time interval after death increased. In many instances the dog hearts perfused immediately after death resumed vigorous rhythmic contractions with the onset of coronary perfusion. Since no human hearts were obtained earlier than 1½ hours after death, comparisons of flow could not be made with the dog hearts studied in this early period. A comparison of the coronary arterial flows at 1½ to 6 hours after death, however, revealed similar values in both human and dog hearts (Fig. 2). In both species, coronary sinus return also decreased in relation to the interval after death and represented a progressively smaller percentage of total

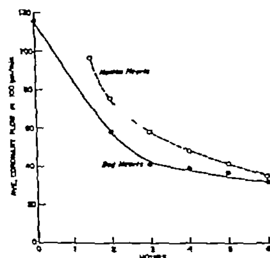


Fig. 2. Effect of time after death on volume of flow through perfused coronary arteries.

coronary arterial flow. Thus, the average ratio of heart weight per 100 ml. of fluid perfused increased with longer intervals after death indicating more edema of the tissue perfused.

Discussion

Much of the available information concerning the characteristics of flow in the human coronary circulation has been derived from studies of hearts obtained at autopsy.[2-7] In many of these investigations, conclusions were based upon data derived from experiments employing coronary arterial perfusion techniques. The present study indicates that definite limitations accompany perfusion of the coronary vascular bed after death and emphasizes that data obtained in this manner must be evaluated with appropriate consideration of these limitations. (1) Resistance to flow in the perfused coronary vascular bed increases progressively with increasing time intervals after death. (2) The proportion of coronary arterial perfusion flow that returns from the coronary sinus significantly decreases with increasing postmortem time. (3) Retention of perfusate in the heart with associated cardiac edema increases markedly as the time after death increases. In addition, after death the normal determinants of coronary blood flow are also greatly altered although these alterations should be very nearly the same in each heart studied.[3] Furthermore the relationship of these postmortem myocardial circulatory alterations and their effects upon cardiac function may prove to be extremely important in the development of techniques for homotransplantation of the human heart.

In 1928 Wearn[4] utilized a coronary arterial perfusion technique to study the myocardial capillary bed. By dye-injection methods he found that the capillary bed was bypassed and did not fill in the perfused nonbeating heart. However he was able to restore rhythmic forceful contractions in human and dog hearts obtained 3 or 4 hours post mortem by perfusing them with an oxygenated Locke-Rosenheim solution and found that the capillary bed filled normally when the heart was beating. He concluded that the rhythmically *contracting* myocardium is very important to the distribution of coronary flow perfusion of the myocardial capillary bed and consequently the cellular function of the heart. Several investigators have demonstrated that human hearts treated with various perfusion techniques can recover ventricular contractions as late as 6 hours after death.[5,6] Redo and associates[7] utilized the isolated-perfusion technique to evaluate the function of guinea pig hearts removed after the animals' deaths, and reported that mechanical activity could be restored to these hearts up to 60 minutes post mortem but that contractile function was severely impaired in hearts reconstituted later than 15 minutes after death. These investigators concluded that severe and often irreversible myocardial changes occur as early as 15 minutes after death and indicated that, unless the myocardium could be protected from these changes, these hearts would function poorly and be unsuitable for transplantation procedures.

The normal values for coronary arterial flows and coronary sinus return have been well documented in the dog by Gregg.[8] Total coronary blood flow values in the canine heart range between 50 and 100 c.c. per 100 grams of heart weight per minute and the coronary sinus return represents approximately 70 per cent of total coronary flow. Several indirect methods have been used to measure coronary blood flow in

man and the results of these determinations indicate that flow values vary from 40 to 160 ml. per 100 grams of heart weight per minute with an average of 100 ml. per 100 grams of heart weight per minute. In the present studies the volume of flow through the coronary arteries of the dog heart during perfusion is essentially normal in hearts perfused immediately after the animals deaths. *However there is a gradual diminution in the amount which may be perfused through the coronary circulation at identical pressures with the passage of time.* In the dog these data indicate that at *6 hours after death* the volume of flow perfused through the coronary vasculature at identical pressures is approximately *one fifth* that which was perfused immediately after the animals deaths. Although we have no perfusion data on human hearts at less than 1½ hours after death the results of coronary perfusion studies performed on human hearts obtained between 1½ and 12 hours post mortem closely parallel those of studies made on dog hearts. The progressive decrease in coronary arterial flow coronary sinus return and the increase in heart weight concomitant with cardiac edema were time dependent on postmortem changes and were similar in both human and dog hearts. The precise mechanisms involved in the development of these postmortem alterations are poorly understood however considerable speculation can be made from Wearn's studies[6] and the experiments presented here. Wearn demonstrated conclusively that the capillary bed filled poorly in the nonbeating heart and postulated that flow bypassed the capillary bed and coronary sinus system entered the arteriolumi nal and Thebesian vessels and subsequently emptied into the ventricular and atrial cavities. It is also well recognized that progressive increases in capillary permeability cellular death and autolysis occur in the postmortem state and probably result in extravasation of the perfusion fluid causing edema external compression of small vessels, and functional occlusion. These studies indicate that measurements of coronary flow in perfused human and animal hearts obtained at postmortem examination are both qualitatively and quantitatively quite different from flow in the coronary circulation of the normal intact human being or dog. Emphasis is placed on the fact that the time interval between death and coronary perfusion is of great importance in determining the volume and distribution of flow through the coronary vascular bed.

Summary

Marked alterations of flow through the perfused coronary circulation of human and dog hearts obtained at autopsy were observed and found to be dependent upon the duration of the postmortem period. After death the total coronary flow decreases with the passage of time the coronary sinus return declines, and there is a pronounced increase in heart weight as a result of the perfusion. These changes are similar in both the human and dog heart and are gradual and progressive. Data on flow in the coronary circulation obtained from the isolated perfused heart obtained at postmortem examination may be quite different from flow characteristics present in the normal dog or man and should be interpreted with caution.

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The low-frequency response of electrocardiographs, a frequent source of recording errors

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The low frequency response characteristics of ECG preamplifiers have been given relatively little attention in the past as a potential source of error in recording. Such errors may manifest themselves as distortions of slow ECG deflections, particularly the S-T segment and T wave. The importance of accurate reproduction of these deflections in acute myocardial infarctions, myocardial ischemia, effects of exercise, and many other conditions does not need to be re-emphasized.

The significance of an adequate low frequency response of electrocardiographs has been stressed by several investigators,[1] but no systematic investigations on the magnitude of possible recording errors have been reported. Frey,[2] in 1937, gave several illustrative examples of distortions that could occur and concluded that a time constant of 1.0 to 1.5 seconds was necessary for adequate recording. Stoboy and William,[3] in 1954, in a similar study demonstrated that distortions in the ECG could occur if a time constant of less than 2.0 seconds was used. The American Heart Association recommended a time constant of 1.6 seconds.

Since no quantitative data on the magnitude of distortions due to inadequate low frequency response of ECG preamplifiers have been reported, a detailed study of such effects appeared to be indicated. Both normal and abnormal records were included in the investigation because the distortions due to differences in low frequency response depend to a large degree on the wave shapes, which may differ from one subject to the next. As a base line for comparisons, records obtained with a simulated DC (direct current) amplifier system[4] were used, representing high fidelity in the low frequency range.

Methods

Electrocardiograms consisting of 24 normal and 11 abnormal records were taken from a series of 35 subjects. The Frank lead system was used for recording. (For the purposes of this study, the selection of a particular lead system is inconsequential because ECG waves of any lead may be distorted by inadequate preamplifiers.)

These records had initially been recorded with an essentially DC recording system onto FM magnetic tape (see Appendix I). Each record was then recorded through a high pass filter which simulated an AC recording system (see Appendix II) and this output was compared to the

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original waveform. The comparison was always made on the same complex, with the original and filtered outputs simultaneously recorded. The characteristics of the high pass filter were adjustable to permit the low frequency cutoff (3 db down) and the slope or rolloff to be varied independently. Fifteen different low frequency characteristics were used with each record as shown in Fig. 1.

In order to analyze these recordings, they were first digitized using an analog-to-digital converter.[7] The converter output consisted of digital magnetic tape, each record of which held the simultaneous samples of the original and filtered waveform. Fig. 2 is a block diagram depicting the process of conversion.

The digital magnetic tape records were fed into an IBM 7094 digital computer for analysis. The S-T segment and T wave of each record were examined as follows. Amplitude measurements at 4-millisecond intervals were made from the end of QRS (the J point) to the end of T. The differences in these measurements between the original record and the filtered one were used to calculate a mean and standard deviation. Then this time interval was divided in two and a mean and standard deviation were calculated for the first half and second half intervals separately. Finally, the total time interval between the J point and the end of T was divided into four equal intervals, and a mean and standard deviation were calculated for each of these four intervals separately.

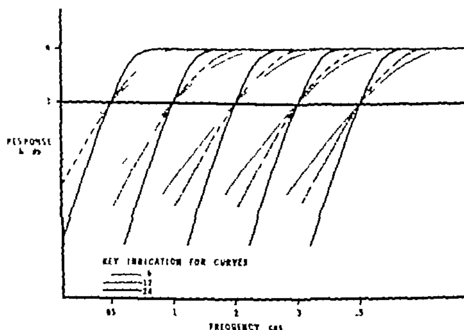


Fig. 1. Frequency characteristics of the 15 high-pass filter systems used to simulate different low-frequency response curves of electrocardiographs. Key indicates slope or rolloff in decibels per octave.

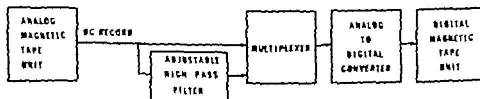


Fig. 2. Block diagram of the analog-to-digital conversion process.

*Table I Percentage of records with errors in the ST T interval exceeding 0 05 0 10 and 0.20 millivolt**

	Rolloff in db./octave	Low-frequency cutoff in c p.s				
		0 05	0 10	0 20	0 30	0 50
First quarter of ST T interval	6	0-0-0	6-3-0	17-11-0	20-11-3	43-20-9
	12	0-0-0	6-0-0	17-6-0	26-11-0	60-23-11
	24	11-0-0	17-0-0	43-17-0	80-34-9	80-57-20
Second quarter of ST T interval	6	6-0-0	6-0-0	11-3-0	20-6-0	20-11-0
	12	3-0-0	6-0-0	14-0-0	20-6-0	34-14-3
	24	11-0-0	14-3-0	31-6-0	43-20-6	60-37-11
Third quarter of ST T interval	6	3-0-0	3-0-0	11-6-0	9-9-3	23-9-3
	12	3-0-0	3-0-0	6-3-0	11-9-0	34-9-3
	24	3-0-0	6-3-0	31-6-3	51-14-9	66-40-14
Last quarter of ST T interval	6	3-0-0	9-0-0	14-6-0	20-9-3	46-14-3
	12	3-0-0	6-0-0	9-0-0	23-3-3	54-26-6
	24	14-0-0	31-6-0	46-11-6	60-43-9	80-57-26

*The percentages of records with errors in the ST T interval are listed here for recording systems with different low frequency characteristics. The three numbers for each entry refer to errors exceeding 0 05, 0 10, and 0 20 millivolt, respectively

Results

The measurements made in this manner revealed some very interesting characteristics (1) Of the 11 abnormal and 24 normal electrocardiographic waveforms, the abnormal recordings were more readily distorted than the normal ones when fed through the filters. (2) The S-T and T portions of those records having essentially monophasic QRS patterns were more readily distorted by the filters than were records having biphasic QRS patterns. (3) In almost all cases, the distortions that did occur showed up as depressions of the S-T segment at the J point, and gradually became less depressed as time increased reaching zero and sometimes becoming elevated in the T wave area.

The number of records containing errors remained approximately the same throughout the entire ST T* time interval However since changes in the S-T segment and T wave are usually considered to have a different diagnostic significance the results have been separately presented for four equal time intervals over the S-T segment and T wave of each record in Table I This table lists the percentage of records out of a total of 35 having amplitude errors in the ST T segment exceeding 0.05 0.10 and 0 20 millivolt, represented by the three consecutive numbers for each item Thus in using a recording system having a low frequency characteristic of 0 2 c.p.s. cutoff and a 6 db per octave rolloff for example, 17 per cent of the records exhibited errors in the first 25 per cent of the ST T time interval in excess of 0 05 millivolt 11 per cent had errors in excess of 0 10 millivolt, and none had errors greater than 0 20 millivolt

In order to test direct writing electrocardiographs in routine use several recorders of different manufacturers were randomly selected from this hospital for performance tests in the low frequency range.

Except for one instrument here for evaluation and not yet in routine use all of them exhibited cutoff frequencies between 0 03 and 0 08 c.p.s. with 6 db. per octave rolloffs. It would seem therefore that the time constant recommended by the American Heart Association is being met by most manufacturers of electrocardiographs.

In the analysis of ECG exercise tests,

*ST T time interval refers to the time interval between the end of QRS and the end of the T wave.

the S-T segment is most important in the interpretation of results, and significance is attributed to S-T depressions of 0.05 and 0.1 millivolt. Telemetering systems for this application are gaining widespread acceptance because it has been stated that exercise tests in some patients may be positive only during exercise but negative in the postexercise period.[8] The literature on a number of commercially available instruments was obtained and the low frequency characteristics of these telemetering systems are listed in Table II. (One of these systems was subsequently tested in this laboratory and found to be in agreement with the manufacturer's specifications.)

Of the six available instruments reviewed solely on the basis of the manufacturers' own literature, all but one failed to meet the present recommendation of the American Heart Association on low frequency response, and at least three of them would be likely to produce S-T distortions in a high percentage of records. For example, the use of instrument "D" would cause 43 per cent of the records to exhibit errors in excess of 0.05 millivolt in the first 25 per cent of the ST-T segment.

Since the distortions produced by inadequate low frequency response are greater in general for abnormal than normal electrocardiographic waveforms, the figures listed in Table I are obviously dependent on the sample of waveforms selected. Of the 35 waveforms that were studied, 24

Table II. Manufacturers' literature pertaining to the low-frequency characteristics of ECG telemetering equipment

Manufacturer	Low-frequency cutoff (3 db down) in c.p.s.	Low-frequency rolloff in db/octave
A	0.10	6
B	0.14	6
C	0.50	Not stated
D	0.50	6
E	0.20	Not stated
F	0.12	12

Table III. Number of distorted records produced when recording with a 0.5 c.p.s. 24 db per system demonstrating how abnormal ECGs are more readily distorted than normal ones

	Degree of distortion: Large (over 0.15 mv.)	Moderate (0.10 to 0.15 mv.)	Slight (below 0.1 mv.)
First 25 per cent of ST-T			
Number of normals	0	9	15
Number of abnormals	8	0	3
Second 25 per cent of ST-T			
Number of normal	0	4	20
Number of abnormals	4	1	6
Third 25 per cent of ST-T			
Number of normals	0	7	17
Number of abnormals	2	1	8
Fourth 25 per cent of ST-T			
Number of normals	6	6	12
Number of abnormals	2	2	7

were considered to be normal and 11 abnormal including cases of acute and old infarcts, ventricular hypertrophies, and conduction defects.

In order to arbitrarily classify distortions as large, moderate, and slight, the magnitude of distortions at 0.5 c.p.s. cutoff frequency and 24 db per octave rolloff (the poorest low frequency response filter) was used as a criterion. A record was classified as being largely distorted when the error exceeded 0.15 millivolt during the first quarter of the ST-T segment, moderately distorted when the error was between 0.10 and 0.15 millivolt, and only slightly distorted when the error did not exceed 0.10 millivolt. On the basis of this criterion, large distortions occurred on 8 of the 11 abnormal records and on none of the normal ones; moderate distortions occurred on 9 of the 24 normal records, and the other 15 normal and 3 abnormal records showed only slight distortions. Table III shows this in tabular form together with the distortions that took place during the rest of the ST-T segment. Only during the later part of the ST-T interval did the distortions appearing in the normal records exceed those in the abnormal records. However, the early portion of the ST-T segment is usually considered to be more significant diagnostically.

Figs. 3 and 4 are examples of the kinds of distortions that do occur when inadequate low-frequency response is used for recording.

Fig. 3 is the X lead of a patient with acute myocardial infarction with an elevated S-T segment. The filtered record has distorted this by reducing the elevation and producing an inversion of the terminal part of T.

Fig. 4 is the Y lead of a patient with an old infarct, showing a downward sloping S-T segment. The filtered record has converted this into an upward sloping S-T segment, which may be interpreted differently.

On a number of normal records the X and Y leads, having essentially monophasic QRS shapes, exhibited depressions in the S-T segment, whereas the Z lead having a biphasic QRS shape did not. Since the X and Y orthogonal leads are similar to



Fig. 3. Oscilloscope photograph of acute infarct record. The DC record (higher elevation of S-T) and the filtered one, displayed simultaneously, were lined up to allow coincidence of the base line between P and Q. In this figure and in Figs. 4-8 the lines of the oscilloscope grid indicate 0.33 mv. in the voltage axis and 0.1 sec. in the time axis. In this and in Fig. 4 the filter used was 0.5 c.p.s. at 6 db. per octave.



Fig. 4. Oscilloscope photograph of old infarct record, showing distortion of the S-T segment in the filtered record. The DC record has the downward sloping S-T segment. (Filter as noted in legend to Fig. 3.)

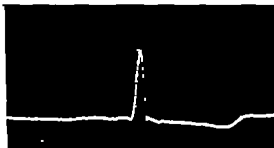


Fig. 5. Oscilloscope photograph of type II monophasic QRS complex, where S-T segment is readily distorted, with inadequate low-frequency response recording.

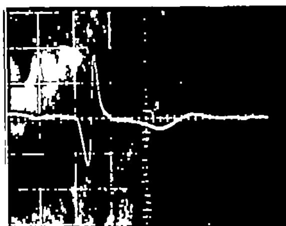


Fig 4 Oscilloscope photograph of typically biphasic QRS pattern where S-T segment is not readily distorted when recording with inadequate low frequency response

the standard leads I and V₆, and aVF II and III respectively it can be expected that all or most of these standard leads would be recorded with S-T depressions Fig 5 represents an electrocardiographic waveform essentially monophasic that is more likely to become distorted when inadequate low frequency response is used than that shown in Fig 6 which has generally a biphasic QRS complex.

Since S-T changes in postexercise records are evaluated mainly in comparison with tracings obtained at rest it may be argued that a recorder with inadequate low frequency response would exhibit errors already in the base-line tracing No additional equipment error would be introduced after exercise. In other words S-T changes of truly cardiac origin should be discernible as being superimposed upon the original instrumentation error

In the investigation of this phenomenon six leads were studied before and after exercise using a 0.5 c.p.s. cutoff frequency with a slope of 24 db per octave. It was found that the increase in heart rate which is seen almost invariably after exercise changed the recording error in an unpredictable fashion as shown in Figs. 7 and 8 For instance in one lead (Fig 7) an error seen in the record taken at rest decreased after exercise. In another lead (Fig 8) the opposite occurred with an error developing only after exercise.

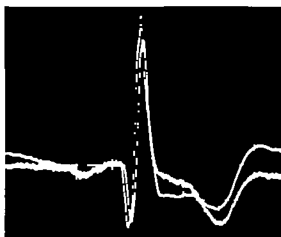


Fig 7A Oscilloscope photograph of Z lead—Resting ECG Filtered record has produced a significant S-T depression (*Note* In Figs. 7 and 8, the filter used was 0.5 c.p.s. at 24 db per octave The reason for the filtered record appearing smoother and exhibiting a slight delay and loss of amplitude in the QRS complex as compared to the DC record is that the high-frequency response was reduced to 50 c.p.s. as compared to 1 000 c.p.s. for the DC record In order to permit better visual comparison of the two traces.)

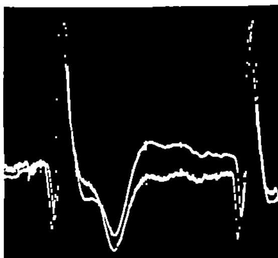


Fig 7B Oscilloscope photograph of same lead as in Fig 7A after exercise S-T depression of filtered record is reduced but still apparent.

The latter tracing showed a biphasic QRS complex.

Discussion

Reference to the data in Table I will show that as expected either an increase

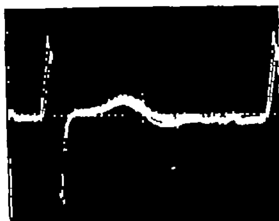


Fig 8A Oscilloscope photograph of V lead of patient—Resting ECG Filtered and DC record show no significant difference. (See Note in legend to Fig 7A)



Fig 8B Oscilloscope photograph of same lead as in Fig 8A after exercise. Filtered record produced significantly elevated S-T segment as compared to the DC record

in the cutoff frequency or a steeper slope will generally result in greater errors in the ST T segment. The present recommendations of the American Heart Association call for a minimum time constant of 1 6 seconds. Although this wording leaves unspecified the slope of the frequency characteristic if one assumes a 6 db per octave slope this is equivalent to a 0 1 c.p.s. cutoff frequency Present day interpretation of electrocardiograms permits an adequate visual resolution in amplitude of 0 10 millivolt. An accuracy of 0.05 millivolt is debatable. However since the trend in electrocardiography is to study the waveforms in greater detail with the use of better recording systems and/or computer analysis, it would seem to be appropriate to use a 0 05-millivolt error as a minimum criterion for evaluating the fidelity of recording systems. With this criterion reference to the data shows an average of 6 per cent of the records exceeded the 0 05-millivolt error throughout the ST T segment when a 0 10 c.p.s. cutoff frequency at a 6 db per octave rolloff was used The use of a 0 05 c.p.s. cutoff frequency reduced this average to 3 per cent of the records and for the first 25 per cent of the ST T complex, the S-T segment proper none of the records had errors exceeding 0 05 millivolt.

Since most commercially available electrocardiographs have a low frequency cutoff at 0 1 c.p.s. with a rolloff of 6 db per octave it can be concluded from the results of this study that in the routine recording of electrocardiograms the first quarter of the ST T complex may be distorted by more than 0 05 millivolt in 6 per cent of the cases, and that in 3 per cent errors in excess of 0 1 millivolt have to be expected Reducing possible errors by 50 per cent should justify new recommendations for low frequency characteristics as outlined above.

It is interesting to note that the use of a recording system having a low frequency characteristic of 0.1 c.p.s. and 6 db per octave, corresponding to the present American Heart Association recommendations, does lead to distortions in the ECG When such a recording system was used for example, 2 of the 11 abnormal records exhibited errors greater than 0 05 millivolt during the first quarter of the ST T interval. (Application of the t test demonstrated significance at the 5 per cent level) In contrast, none of the normal records displayed errors of this magnitude during this same period. From such a small sample it is not possible to accurately predict the percentage of records which would give rise to distortions. However it is reasonable to infer from these results that errors

*Specifically the American Heart Association report states that "The response of the instrument at 0 2 second after the application of a direct voltage of 1 0 millivolt shall not deviate more than ± 10 per cent from the response at 0 04 second

greater than 0.05 millivolt are likely to occur in a significant number of abnormal records when the presently recommended minimum low frequency recording characteristics are used.

Using equipment available at present, the electrocardiographer has to realize that in a small percentage of cases an S-T shift of 0.05 millivolt or even of 0.1 millivolt may be due to the performance characteristics of his recorder. Although the incidence of such errors is relatively low for most recorders, in some others it is found more frequently. Ideally, records with a DC response should be used for some high fidelity recording of low frequency phenomena. The frequent base line drifts of DC preamplifiers has made such recording impractical up to now. Until this difficulty can be overcome, the electrocardiographer has to live with the best possible compromise. The recommended cutoff at 0.05 c.p.s. with a slope of 6 db per octave did not appear to influence appreciably the S-T segment proper and distorted only the T wave in a very small percentage by less than 0.1 millivolt. It is rather unlikely that this small and infrequent error in T wave reproduction can lead to erroneous ECG interpretations in records taken at rest.

In exercise electrocardiograms, the use of recording equipment with inadequate low frequency response, such as with some telemetry equipment, may result in recording errors in either the resting or the exercise record or in both. As shown in Figs. 7 and 8, a change in heart rate alone may alter the S-T configuration appreciably when an inadequate low frequency response is used. Such artifacts were almost unpredictable since they were found both with an increase and with a decrease in heart rate. Adequate low frequency characteristics should make such errors negligible. They are extremely critical, however, for most telemetering units which have been gaining wider acceptance for recording during exercise. As shown in Tables I and II, some of these units may lead to S-T recording errors in excess of 0.05 millivolt in more than 40 per cent of the tracings, and in excess of 0.1 millivolt in 20 per cent. Superimposed on these artifacts in an unpredictable fashion are the S-T recording errors which are due solely to changes in heart rate. Therefore one cannot discount inadequate low frequency response of telemetering systems simply because the resting ECG for reference is recorded with the same poor system.

Summary

A detailed study of the effects of inadequate low frequency response was made on 35 normal and abnormal electrocardiograms. Each record, after being recorded with a system whose low frequency characteristics were known and adjustable, was compared with its DC recording on the same complex. Computer measurements of amplitudes in the ST-T complex were obtained.

Inadequate low frequency response is capable of producing S-T shifts in a variety of electrocardiographic waveforms. Waveforms with essentially monophasic QRS patterns are more likely to be recorded with significant distortions. The distortions usually show up as depressions during the early portion of ST-T, gradually becoming less depressed and sometimes becoming elevated at the terminal part of T.

The amount of distortion is dependent on the cutoff frequency and rolloff. To insure that errors do not exceed 0.05 millivolt in the early part of the ST-T complex, a 0.05 c.p.s. cutoff frequency with a 6 db per octave rolloff should be used in recording. Although it appears that the present recommendations of the American Heart Association are being met by the manufacturers of most direct writing electrocardiographs, it seems to be appropriate to better define the low frequency response in terms of frequency and slope rather than (or in addition to) time constant.

A review was also made of low-frequency characteristics of ECG telemetering units which are being used for recording during exercise. The majority of these units was found to deviate considerably from recommended instrument specifications, and artifacts can be expected in a sizable percentage of recordings. In addition, S-T recording errors were also found with changes in heart rate.

Appendix I

If the response characteristics of an AC recording network are known, it is possible,

Fig. 9 Block diagram of typical ECG preamplifier showing RC coupling between tages which determine its AC response characteristics. The general form of the frequency response of such a preampl fier is show In the lower half of the figure.

Fig 10 Block diagr m of network used to resynthesize signal t rest the low fr q ncy haract with frequency response of this netw [illegible]

in principle, to construct a network having a response characteristic such that a signal passing through both networks will behave as though it were passing through a DC system. This resynthesis of a signal can be accomplished as follows[4]

A conventional ECG preamplifier consists of one or more RC coupled stages which determine the time constant (or low frequency response) of the system. Fig. 9 illustrates such a preamplifier. If an ECG is recorded on FM analog tape using such a preamplifier system, it will be degraded more or less depending on the time constant. However, in playback, the signal can be passed through a network shown in Fig. 10 having characteristics opposite to that of the recording system. Thus the low frequency characteristics of the original signal will be restored. Obviously the accuracy will depend on how well the recording characteristics are known and to what degree they are compensated for in the playback network. In general, each RC time constant of the compensating network should be made equal to each RC time constant of the interstage coupling in the recording preamplifier.

In this study, the recording preamplifier had a low frequency cutoff of 0.10 c.p.s. with a 6 db. per octave rolloff. After recording onto tape, the reproduced signal was fed into a network with a single RC time constant, similar to one stage of the network shown in Fig. 10. This arrangement allowed for an over-all frequency response from preamplifier input to tape output of better than 0.01 c.p.s. (we were unable to test the system below this frequency) and this was deemed to constitute an essentially DC system.

Appendix II

In order to simulate the low frequency characteristics of a typical electrocardiograph, an operational amplifier with appropriate RC networks was chosen to behave as a high pass filter. The R and C values were selected to obtain the desired cutoff frequency. Fig. 11 shows the setup used to obtain various low frequency cutoffs with a 6 db. per octave slope, and Fig. 12 shows the setup for obtaining the 12 db. per octave slope characteristics. A standard Krohn-Hite filter was used to obtain the 24 db. per octave recordings.

In the case of the 6 db. per octave roll

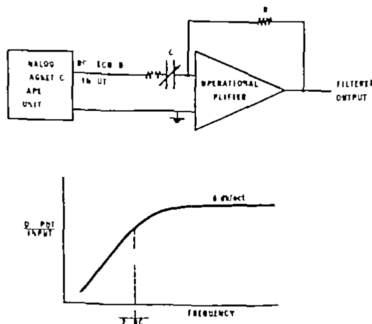


Fig. 11. Simulation of 6 db. per octave low-frequency characteristic of a typical electrocardiographic recording system.

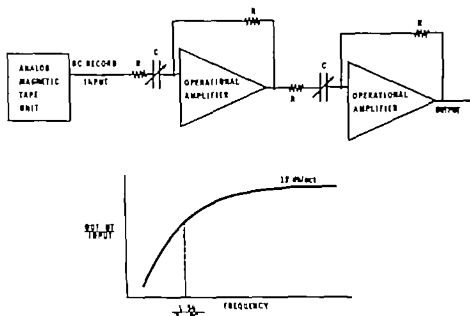


Fig. 12. Simulation of 12 db. per octave low-frequency characteristic of a typical electrocardiographic recording system.

off the value of R times C is adjusted such that the final output is attenuated 3 db at the desired frequency according to the formula

$$f_{3db} = \frac{1}{2\ RC}$$

Using two operational amplifiers to obtain the 12 db per octave rolloff each R times C value is adjusted such that the final output is attenuated 3 db at the desired frequency according to the formula

$$f_{3db} = \frac{1.56}{2\ RC}$$

In both cases the high frequency gain is unity since the feedback resistor is equal to the input resistor.

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High fidelity electrocardiography: Effects of induced localized myocardial injury in the dog

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The incidence of high frequency notching in the QRS complex of patients surviving myocardial infarction has been found to be much greater than in normal control subjects.[1-4] In some instances, high frequency notching has been the only residual electrocardiographic abnormality after recovery from an infarct.[4] Burch and his colleagues found notching in the vectorcardiogram of subjects who at autopsy had patchy fibrosis or necrosis of the myocardium.[4] Durrer and his co-workers demonstrated abundant high frequency notches and slurs in the electrocardiograms of dogs and isolated revived human hearts after experimental coronary occlusion.[7,8] In his canine experiments, Durrer found, after this severe injury, irregularly shaped fibrotic myocardial scars. Both of these studies concerned myocardial lesions of substantial extent, and the notching of the QRS was usually accompanied by additional changes in the electrocardiogram.

It is the purpose of this study to create a small area of injury in the free wall of the left ventricle in order to determine whether this will cause a discrete notch or slur in precordial leads, and, if so, to investigate whether electrodes overlying the limited segment of myocardial injury will best reveal it. Such findings would lend further support to the explanation of Burch and of Durrer for the cause of notching in the QRS.

Material and methods

Nine mongrel dogs, weighing from 10 to 15 kilograms, were used. Each one was anesthetized by an intravenous injection of pentobarbital (approximately 35 mg. per kilogram of body weight), then placed on its right side, and the left chest was closely clipped and marked with a grid as shown in Fig. 1A. The trachea was intubated. Control electrocardiograms were taken from each of the 36 intersecting points of the grid shown in Fig. 1A.

To produce the injury, approximately 0.1 c.c. of a toxic mixture was injected into the myocardium through a 16-gauge needle 9 cm. in length. This mixture had the consistency of a paste and contained a destructive agent, formalin, a radiopaque

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material barium sulfate and lamp black which would be visible to the naked eye when the heart was subsequently sectioned

In the first experiment, a thoracotomy was performed initially in order to determine the optimum manner in which a localized lesion could be produced in the heart wall. An approach entering the thorax at the third or fourth left intercostal space and proceeding dorsocaudad to enter the epicardial surface of the left ventricular wall tangentially was found to be most satisfactory.

In the other 8 dogs a closed-chest procedure was used as follows. An incision was made in the skin at a preselected site and the parietal pleura was reached by blunt dissection. Then a close-fitting polyethylene sheath was put over the needle, leaving a variable length of the tip of the needle free to enter the myocardium (usually 1 cm.). The sheathed needle was inserted between the ribs, piercing the pleura. The sheath was then extended over the tip of the needle for safe maneuverability. Thus, puncture of the lung with consequent pneumothorax and inadvertent severing of the anterior descending coronary artery were avoided. Under fluoroscopic guidance the tip of the needle was directed to the desired location in the heart wall and inserted into the myocardium.

A control electrocardiogram was taken from the hub of the needle to make certain that the myocardium had been pierced as manifested by marked S-T segment elevation (about 30 mv.) due to acute subepicardial injury at the site of puncture of the heart. Then the needle load was injected and immediately afterward a radiogram was recorded in order to determine the presence and location of the injection and to show that the heart was in the same position as in the control period. The needle was withdrawn and postinjection electrocardiograms were recorded repeatedly at 15-minute intervals over the points of the chest grid which is shown in Fig. 1A. This figure is a drawing of the principal structures of the x-ray film shown in Fig. 1B plus a typical grid which was drawn on the left chest wall of each dog. Electrocardiograms were made from the skin at the 36 intersection points of this grid. The points on the grid were numbered 1 to 6 in the first column going from dorsum to sternum then 7 to 12 in the next column and up to 31 to 36 in the sixth or last column. The five numbers in parentheses represent sites at which radiopaque barium was seen after successful injection of the toxic mixture into the left ventricular wall of 5 dogs as previously described. The outline of the heart shown in Fig. 1A and

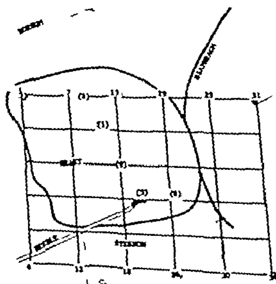


Fig. 1A. Schematic drawing of chest x-ray film shown in Fig. 1B with superimposed precordial grid with lines approximately 1 inch apart (see text).



Fig. 1B. Chest x-ray film of Dog No. 5, an example of transthoracic needle injection into intramural myocardium (see text).

in the x ray film in Fig 1B as well as the other anatomic structures varied to a moderate degree in different dogs depending upon the size and build of the animal In Dog No 8 the injection which at first was thought to be in the free left ventricular wall proved on sectioning the heart to be in the intraventricular septum This occurred because of rotation of the heart so that the left ventricle was more dorsal than usual plus the fact that the needle had been directed almost perpendicularly to the heart wall

In the last 2 experiments a more caustic injection composed of 0 1 c.c of 40 per cent formalin placed between strata of the paste was used The lower third of a 16-gauge needle was filled with the paste and about 0 1 c.c of formalin was injected into its upper part. A 2-c.c syringe containing more paste was attached to the needle in order to make the injection This preparation which again produced a discrete localized lesion was found to cause much more severe and widespread notching on the precordium than did the toxic paste alone In these 2 experiments the procedure was the same as in the preceding 6 dogs except for the use of more 40 per cent formalin

Fig 2 illustrates the type of lesion caused by the injection A block of myocardium approximately 3-cm square including the area of injury was removed The needle puncture was at the center of the epicardial surface of this block. This block was sectioned perpendicularly to the direction of the needle and opened out so that both of the cut surfaces were lying nearly flat, facing upward Thus, Fig 2 shows two needle punctures going through the intramural myocardium and the lamp black appearing at the junction of the cut in the myocardial wall outlines a cross-sectional area of the injected material

The electrocardiograms were taken with an Electronics for Medicine, Model No. DR8 oscilloscope recorder employing 5 channels, with a paper speed of 200 mm. per second and a frequency response flat from 0 1 to 2 000 cycles per second The standardization of the precordial complexes was 10 to 20 mm per millivolt depending on the size of the QRS amplitude. The standardization of complexes



Fig 2 Gross section of heart wall showing extent of an intramural injection. The white material appearing in the upper half of the picture is surgical cotton supporting the upper flap of myocardium

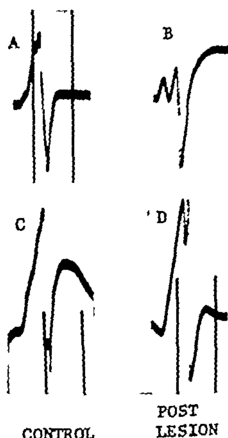


Fig 3 Control and postinjection epicardial electrocardiograms from the open-chest preparation. Complexes B and D were simultaneously recorded (see text).

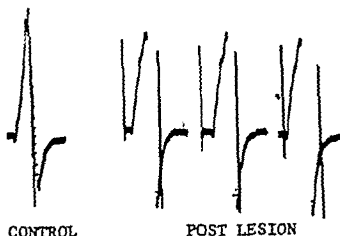


Fig. 4 High-frequency slurring caused in a precordial lead in Dog No. 6. Three successive post lesion QRS complexes are mounted to show the repetitive similarity of the slurring.

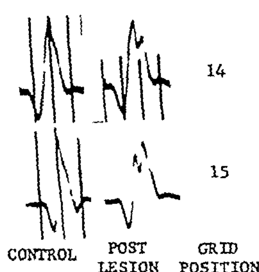


Fig. 5 Intermediate-frequency notch produced in precordial leads from grid points 14 and 15 in Dog No. 9 (see text).



Fig. 6 Intermediate-frequency notch in a precordial lead caused by the septal injury in Dog No. 8 (see text).

taken directly from the epicardium could not be measured accurately but was a fraction of a millimeter per millivolt. The cross-hatching usually seen on electrocardiograms to give a time and amplitude scale was not used in this experiment in order to avoid any obscuring of the notching in the QRS by these lines. Vertical time scale lines were retained in the lower half of the paper. These are seen with most of the QRS complexes, but not all. The interval between the vertical lines was 0.04 second in Figs. 3 and 4, and 0.02 second in Figs. 5 and 6.

Results

Clear-cut notching either high or medium frequency in character was produced in 6 of the 9 dogs, and it always appeared within 15 minutes of the cardiac injection and persisted during the following 2 hour period of observation. In the first dog (the open-chest preparation), injection of toxic paste into the myocardium approximately at the center of the left ventricular surface caused the short-duration (i.e., high-frequency) notch in an epicardial

lead as shown in Fig 3 (complex *D*) This lead was from a point over the damaged area. Subsequent ligation of a small branch of the anterior descending coronary artery directed toward the apex of the left ventricle produced the broad (low frequency) notch seen in Fig 3 (complex *B*) recorded from an apical epicardial lead This was the only coronary ligation performed in these experiments. The contrast between the effects seen in complexes *B* and *D* shown in Fig 3 is noteworthy The fact that the defect of the QRS recorded from the apex (complex *D*) precedes the fast notch (complex *B*) recorded from the upper more dorsally located area of damage is to be expected from previous work on the sequence of ventricular depolarization [10,11] Possible explanations for the cause of the small notch at the peak of the R in the QRS of complex *A* before deliberate injury and the possible reason for the S-T elevation in complex *C* are both conjectural and beyond the scope of this paper

Fig 4 (Dog No 6) illustrates an excellent example of high frequency slurring in the upstroke of the precordial R wave from point 22 on the grid (Fig 1*A*) caused by a small injection near the apex in the left ventricular wall

Fig 5 (Dog No 9) shows notching of intermediate frequency in the QRS recorded from points 14 and 15 on the precordial grid Point 15 was immediately over the site of injection in the left ventricular wall It is very significant that these notches in Figs. 4 and 5 were always most prominent in the leads from points immediately overlying the site of the lesions in the heart. Furthermore, in all cases the notching faded out rapidly as one moved the point of the chest probe from the location of optimum effect (i.e., within a 2 inch radius) In Fig 5 the notch occurred earlier in the QRS of the record taken from the precordium nearest the myocardial injury

The notching caused by the septal injection in Dog No 8 was of intermediate frequency in character and is shown in Fig 6 as it appeared in the precordial lead from the number 9 grid position

In 4 instances, dogs were examined 1 week after the initial experiment In 1 animal the notching that was still present 2 hours after injection had disappeared completely In the other 3 the notching persisted with little or no change.

In Dog No 2 no notching was produced on any precordial electrocardiograms and at autopsy it was found that the needle had made an entrance into and also an exit from the heart wall at the epicardial surface and that the injection pellet was extracardiac in the pericardial sac It is of interest that the needle puncture per se, was not a sufficient injury to produce a notch in the precordial electrocardiogram In Dog No 3 an anesthetic death occurred after injection of the chemical mixture before sufficient records could be taken In Dog No 7 the records were marred by artifacts and could not be used for study

Discussion

The primary purpose of this preliminary experiment was achieved that is the production of notching and slurring in the electrocardiogram as a result of induced localized myocardial lesions which did not result in Q-wave or ST T changes or any other diagnostic changes in the precordial electrocardiogram Although approximately the same amount of injectable material was used the size and shape of the area involved varied as shown by x ray films in vivo and by the distribution of lamp black after sectioning of the hearts. In some cases the paste remained in a relatively small compact area whereas in others it was more diffusely spread through a slightly larger area among the muscle bundles of the heart wall. The extent of the electrical damage was assumed to be confined to the tissue within the immediate vicinity of the injection of toxic paste. Abildskov and associates,[12,13] after local injection of 40 per cent formalin and India ink into the myocardium found histologically that tissue damage did not extend beyond the area stained by India ink. The total amount of formalin in all but the last 2 of our injections was less than that used by Abildskov and his colleagues, who produced more extensive changes in the electrocardiogram However in one of their papers there is a new high frequency notch seen in the initial portion of the QRS of a

Z lead (See their Figure 4b labeled "Post Lesion."[11])

In the 5 successful experiments on closed-chest dogs the induced myocardial lesion caused notching in the QRS recorded from an area having a radius of 1 to 2 inches on the left thoracic wall overlying the damaged portion of the heart. The frequency content (i.e. duration) of the notching produced was found to cover the full frequency spectrum of the notching previously described in human electrocardiograms.[2,14]

A very general statement as to the cause of notching is that a smooth wave front of ventricular depolarization either approaching or receding from the exploring electrode is desynchronized or fragmented.[3,4]

To provide a simple explanation of a notch consider the genesis of the upstroke in the R wave using Precordial Lead V_4 as an example. The upstroke of the precordial R wave is produced by electrical forces in the heart which are directed toward the exploring electrode. These forces can be most conveniently represented by a vector varying with time. As the normal smooth R wave is written the vector magnitude increases with time until the peak of the R is reached. If a section of the myocardium underlying the V_4 electrode position fails to contribute to this smooth propagation of the wave of depolarization a notch may be produced in the QRS by momentary preponderance of oppositely directed electrical forces elsewhere in the myocardium.

According to time-honored theory most septal forces in normal hearts of man and dog do not contribute to the electrocardiogram because of mutual cancellation. It is interesting to note that the elimination of some of these forces in Dog No. 8 apparently disrupts the cancellation sufficiently to produce a notch.

The magnitude duration and timing in the QRS and duration of a discrete notch together with the positions on the body surface at which notched complexes are detected can usually be correlated with the size and location of the patch of inert muscle in the myocardium. For instance if "proximity effects" are demonstrable the position of the exploring electrode from which the most prominently notched complex is recorded would imply that this exploring precordial electrode points to the nearest segment of myocardium as being the damaged area. In the present experiment, maximum notching was always detected on the precordium immediately over the injured area of the heart wall.

Multiple notching and slurring in the QRS are probably due to a complex mosaic of interspersed islands of electrically active and inert myocardial tissue. On the basis of an analysis of human-body-surface electrocardiograms the existence of such a mosaic can be postulated with some confidence[14] and this is supported by reports of Burch and associates[3,4] and Durrer and associates.[7,8] However the precise location and extent of the myocardial disease responsible for multiple notching in man would require both body-surface ECG–autopsy correlation and more accurate and complete knowledge of the detailed sequence of activation throughout the ventricular myocardium than is now available.

Summary

Small intramural lesions were successfully produced in the myocardial wall in 6 of 9 dogs. In these 6 dogs, notching of the QRS was found to be maximal in the precordial leads directly over the damaged area of the myocardium. Therefore, one explanation for the derivation of notching in the QRS is the disruption of the usually smooth depolarization wave. This finding supports the explanations given for the cause of multiple notching found in the abnormal electrocardiograms of human patients.

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Potassium and experimental coronary occlusion

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Potassium bears an important relationship to the consequences of coronary occlusion because of liberation of this ion from cells of the ischemic portion of the myocardium and the evident influence of regional increase in K upon the generation of ectopic arrhythmias. Abrupt ligation of the anterior descending artery of the dog heart at a judiciously chosen high level is usually followed by ectopic ventricular activity. This activity occurs in a phasic pattern, beginning with a *first* phase which begins, passes its maximum, and declines in almost all experiments within the period of 2½ to 15 minutes after occlusion and may produce ventricular fibrillation.[1] Survivors then pass through a period of 4½ hours or longer (*second* phase) of sinus rhythm with no premature beats or only an occasional ectopic complex. After this quiescent period, ectopic complexes again appear or, if present, begin to increase in frequency (initiating the *third* phase). The increase then is marked and progressive from one half hour to the next, usually producing a complete ventricular tachycardia, heterotopic in origin, within 8 to 12 hours after occlusion.[1-4] The ectopic discharge rate of the ventricular tachycardia reaches a maximum and slowly subsides to complete cessation of ectopic activity after 48 to 72 hours in a majority of dogs, but has continued for as long as 120 hours.

The portion of the ventricular myocardium that is deprived of circulation quickly begins to undergo changes in composition, which include migration of K from the interior of cells and the passage of Na and water into them.

Hypothesis that local liberation of K is an important factor in ectopic excitation during early ischemia and necrosis. Measurements of electrolytes from samples of blood plasma obtained from a local vein within the ischemic region offer the closest available approximation to concentrations that exist in interstitial fluid enveloping the ischemic myocardial cells, although the concentration of K at the cell surface must be somewhat higher than that of the plasma. The concentration of K in such locally obtained samples exhibits a pattern of changes with time which parallels to a degree suggestive of a causal relationship the time pattern of occurrence of ectopic activity during the first 5 hours of occlusion and possibly somewhat longer. Samples of coronary sinus plasma have proved to be unsatisfactory for the study of these relationships. Systemic plasma shows little or no change during the early hours of

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occlusion. A K concentration gradient is therefore created between the ischemic region of myocardium and the remainder of the ventricular muscle with normal circulation which adjoins with and surrounds it. This gradient is the basis of the injury potential.

An excess of extracellular K partially depolarizes myocardial cells with which it is in contact, and at levels up to 9 mEq./L. it increases excitability, whereas higher concentrations have a depressant effect.[7]

The boundary that joins the ischemic region of myocardium with the part with normal circulation contains within a narrow span a gradient of increased elevations of extracellular K that range from the control level usually found in the dog's systemic blood, about 3.5 mEq./L., to that which surrounds ischemic cells, undoubtedly greater than the highest level found in the ischemic myocardial venous samples, 6.5 mEq./L.[8]

The elevated concentration of K within a region and the resulting K gradient at the boundary produce two effects that apparently summate to generate ectopic impulses: (1) some boundary cells certainly are exposed to K concentrations within the range that increase excitability to electrical stimulation, and (2) the injury (K) potential produces currents which circulate within this narrow region that contains the hyperexcitable cells. The combined effects then hypothetically cause excitation. Generalized hyperpotassemia produced by the slow intravenous infusion of KCl solution,[7] or generalized hypoxemia[8] which also produces hyperpotassemia, increases excitability but does not generate ectopic impulses. Uniform elevation of plasma K and progressive hypoxemia, when sufficiently severe, produce heart block and arrest, not ectopic ventricular arrhythmias.[3-4]

Injection into a coronary artery of Locke's solution or of blood containing added KCl sufficient to exceed a threshold level of near 3 times the standard Locke concentration at an injection rate of 5 ml. in 20 seconds produces ectopic activity during injection in a percentage of trials, the dependability rising with the concentration of K injected, and ventricular fibrillation can readily be produced by this technique. After injections which evoke ectopic beats but not ventricular fibrillation, the ectopic activity characteristically ceases shortly after termination of injection, but the total effect is not finished so quickly. After a further interval that varies between 5 and 15 minutes, a second period of ectopic activity may begin. Such second periods have occurred in 40 to 50 per cent of trials, including published observations[8,11] and new experiments in progress. The second arrhythmic period that follows a brief injection of K usually has a duration of 3 to 10 minutes after its delayed onset but may last longer. In one trial it ended 34 minutes after injection, 20 minutes after its delayed onset.

The injury potential subsides within less than 1 minute after brief injections of fluid with a near threshold concentration of K. The second period of ectopic activity which begins some minutes later must be due to some factor or factors of excitation that differ in nature from hyperexcitability of boundary tissue acted upon by an injury current. During the period of excessive K concentration which may produce immediate ectopic impulses, an additional process evidently is initiated, a process which develops an excitatory state gradually, and which reaches the ectopic discharge level after a number of minutes. This second process is as yet unidentified. We need to learn whether excess K causes release of myocardial catecholamines after a latency of minutes. No deviation of the S-T segment has been observed to develop with it.

In regional myocardial ischemia during the periods when a high local concentration of K in extracellular fluid exists, both types of excitatory influences mentioned in relation to the intracoronary injections of K probably are active: (a) hyperexcitable boundary cells stimulated by injury current, and (b) the second factor induced more slowly after initiation by excess K.

Further evidences in support of the concept that release of K in a local region of myocardium induces ectopic activity and ventricular fibrillation are provided by the findings of Hano and Harris[12] that injection into a coronary artery of octylamine, a K release agent, is followed by ventricular ectopic activity after the few

minutes required for adequate egress of K to the extracellular fluid. This ectopic activity led to ventricular fibrillation in some trials. When octylamine was injected into a ligated coronary artery distal to the ligature 24 hours after it was occluded no ectopic activity was induced by it. This failure to excite is explained by tissue analyses which show that after 24 hours of ischemia the necrotizing myocardial cells have lost almost all of the K that they formerly contained in excess of the plasma level and the intracellular extracellular concentrations are approaching equilibrium.[11,14] Octylamine perfusing this region then fails to increase local extracellular K and fails to produce excitation.

Protein free extracts of dog myocardium have been reported to produce ectopic excitation when injected into a coronary artery of a normal dog heart.[8] Russell (unpublished data) has recently repeated these experiments, carefully separating infarct from normal tissue and found that extracts made from myocardium of a 24-hour infarct fails to excite whereas extracts of normal myocardium excite with a time pattern of activity which matches that of excess K.

Limitation of duration of probable excitation by K gradient. The rate of migration of K from ischemic myocardial cells is great during the first few minutes of ischemia and again between the third and twelfth hours.[6,11,14] After 12 hours, with only 20 per cent or less of the original intracellular K remaining in the cells migration across the cell membrane becomes slow. A natural corollary is that the boundary gradient must be reduced and gradually lost. Since the ectopic arrhythmia typically is approaching maximal frequency at 12 to 15 hours, and some ectopic activity continues for 48 to 72 hours and sometimes longer excitatory factors other than the K gradient and injury potential other factors arising from products of necrotic cells, and injury to surviving portions continue to be objects of search.

Augmentation of ectopic excitatory action of sympathetic nerve impulses and of norepinephrine by coronary occlusion and by injection of K into coronary arteries. Recent studies have shown that cardiac sympathetic nerve stimulations which rarely produced an ectopic complex in control trials were significantly more effective after occlusion of a coronary artery regularly producing ectopic activity and in some instances paroxysmal ventricular tachycardia and fibrillation.[4] Experiments now in progress have revealed augmentation of the ectopic impulse inducing action of a subthreshold concentration of norepinephrine when infused into a coronary artery 10 minutes after infusion of KCl of near threshold concentration in blood during a period of 1 minute. This norepinephrine augmentor effect of K must be intimately related to the sympathetic nerve augmentor effect of ischemia.

Inhibition of arrhythmias by administration of K. Clinical and experimental reports attest the termination or reduction of ventricular ectopic arrhythmias by the administration of K salts, with particular effectiveness in arrhythmias resulting from the toxic action of digitalis glycoside.[15,16] Coraboeuf and associates[17] found that Purkinje fiber transmembrane action potential during a level of glycoside action which increased rhythmicity exhibited two types of modification that appear to be concordant with the increased automaticity (a) the action potential did not return to the control base line, signifying less complete repolarization and (b) the diastolic depolarization gradient became steeper. The findings of Moe and Mendez[8] that electrical threshold is raised during the most intensely arrhythmic phase of toxic digitalis action obscures the meaning of incomplete repolarization due to digitalis with respect to automaticity. The increase in the diastolic depolarization slope is however characteristic of pacemaker activity and is probably significant. An increase in extracellular K reduces or abolishes this gradient[9] and therefore should reduce or abolish the pacemaker action.

Severely toxic doses of glycoside have been found to produce focal necrosis in dog ventricular myocardium.[19] The presence of local regions of lethal injury suggest a similarity to regional infarction due to ischemia and may indeed create K concentration gradients and local injury currents about such foci. Reduction of a

boundary K concentration gradient by an increase in K in circulating blood plasma should reduce the injury current and the associated excitatory effect. A reduction in the rate of diastolic depolarization of Purkinje fibers within the injury current field also may be a factor.

The administration of large amounts of glucose and insulin just before occlusion of a coronary artery in the dog has prevented, reduced, and delayed the occurrence of ventricular ectopic arrhythmias and fibrillation. This result was correlated with large reductions in K concentrations in coronary sinus and systemic plasma.[11]

Sodi Pallares and collaborators,[12] by the administration of their glucose-potassium insulin (G-K-I or "polarizing") solution to dogs at intervals up to 6 hours after occlusion of the anterior descending artery, have produced early diminution or disappearance of the positive monophasic RS-T elevation, and disappearance of a dip interpreted as a sign of focal block. These changes reappeared after administration of the solution was suspended. The G-K-I solution also terminated ectopic beats 6 hours after occlusion. Analysis of tissue from the infarct region of treated and untreated hearts revealed that there was less loss of K, less gain of Na, and less gain of water in the cells of treated hearts than in those of the controls.

Excitation of nerve fibers and ganglia and skeletal muscle fibers by nonuniform increase in K concentration. Application of KCl solution to posterior nerve roots of the cat by intrathecal injection or by painting it on exposed nerve roots has caused intense reflex responses.[22] A drop of isotonic KCl placed on a squid axon caused a transient discharge of impulses and a steady difference in potential between the point of application and another point on the fiber.[24] Sympathetic ganglia perfused with Locke's solution were stimulated by injecting a small amount of KCl into the perfusing fluid, even after degeneration of preganglionic fibers and a reduction in the liberation of acetylcholine in the ganglion to trace amounts.[25,26] Application of KCl locally to the motor end plate of a single skeletal muscle fiber causes rapid tetanus-like contractions. This response occurs even when the end plate is nonresponsive to acetylcholine because of the former application of acetylcholine and is insensitive to the nerve impulse but still responsive to electrical stimuli. When it fails to react to electrical stimulation, it fails to respond to locally applied K also.[27]

All of the foregoing examples of excitations by K were the results of the application of the K-rich solution to only a part of the neuron or muscle fiber involved. If a segment of excised nerve or a thin muscle is immersed totally into a physiologic saline solution with excess K up to 2 or 3 times normal concentration, excitability will be increased, but usually without the discharge of impulses. Higher concentrations depress, and this effect appears to be better known than that of increased excitability.[11,22]

Discussion

This review has documented the excitation of heart muscle, skeletal muscle, nerve fibers, and ganglion cells by contact of a part of the tissue with fluid containing an increased concentration of K. The probability that a myocardial ischemic-nonischemic boundary (which quickly becomes a high K–normal K boundary) is an important factor in providing conditions that lead to ectopic excitation soon after occlusion of a coronary artery appears to be almost too strong to allow a basis for further argument. Yet argument persists.

The finding that ligation of both the right and left main coronary arteries leads to ventricular fibrillation has been interpreted to mean that inequality of circulation to adjacent regions, or the presence of a boundary, is not essential to the initiation of ectopic impulses due to ischemia.[11,30] Closer examination of the conditions that prevail shortly after occlusion of both main coronary arteries reveals that inequalities of myocardial access to oxygenated blood must exist, and that these inequalities would produce boundaries that undoubtedly last through durations as long as the 2½ to 6 minutes found between double ligation and the onset of fibrillation. The endocardial layer of left ventricular muscle is in contact with the oxygenated blood of the cavity, and this thin oxygenated layer is extended into the walls via the

luminal vessels. A short distance from this irregular layer the myocardium ceases to contract sufficiently to pump blood and becomes deeply ischemic within less than 1 minute. The cessation of pumping undoubtedly tends to cause the oxygenated blood which is held in the left ventricular cavity to maintain its arterial properties for a considerable time, thus maintaining boundary conditions in the locations described, locations that contain and are crisscrossed by a network of Purkinje fibers which are prone to develop autorhythmicity.

Summary

The temporal relationship of regional release of intracellular K ions and consequent local elevation of extracellular K concentration after coronary occlusion to the occurrence of ectopic activity has been reviewed.

The experimental demonstrations that extracellular elevation of K concentration within a limit up to about 3 times normal increases excitability to electrical currents, and that injury current flows into hyperexcitable border regions form the basis of a hypothesis that the discharge of ectopic impulses is evoked or facilitated during the period when these conditions exist. Experiments which show that skeletal muscle, nerve fibers, and ganglion cells also are excited by exposure *in part* to elevated K concentration are cited. Uniform exposure does not commonly produce autorhythmicity.

Administration of K salts may reduce ectopic activity (a) by reducing the rate of membrane diastolic depolarization of cells exhibiting this pacemaker property, (b) by reducing the difference in concentration across the boundary, hence the injury current, and (c) by reducing the electrolyte and water migrations of ischemia, thus maintaining more normal cellular conditions, reported as a result of polarizing solution.

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Case reports

The simultaneous occurrence of ventricular pre-excitation, left bundle branch block, and delayed A-V conduction

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The vectorcardiogram, capable of recording minute changes in the temporal and spatial sequence of ventricular activation, is ideally suited for the demonstration of ventricular conduction disturbances. The individual VCG features of pre-excitation and of left bundle block are well established, but few reports have demonstrated the coexistence of these two disorders of ventricular excitation, which has a statistical probability of 0.024 per cent.[1] In most reported cases of ventricular pre-excitation with bundle branch block, block of the right bundle was the associated finding.[2-4] The following case is an example of the unusual occurrence of homolateral pre-excitation and left bundle branch block, associated with delayed atrioventricular conduction.

Case report

A 67-year-old Negro man was admitted to St. Vincent Hospital on Sept. 19, 1964, because of progressive exertional dyspnea, orthopnea, and ankle edema. Since 1962 he had been hospitalized two times and had made numerous visits to the clinic for the control of left heart failure. All electrocardiograms taken during this time showed a pattern of complete left bundle branch block with QRS duration of 0.14 second, frontal plane mean axis of −30 degrees, and P-R interval of 0.22 second. Q waves were absent in Leads I, AVL, V_5, and V_6; small R waves were present in Leads V_1 to V_3 (Fig. 1,*A*).

The past history included hypertension for 18 years and, in 1953, treatment for syphilis and a subtotal thyroidectomy. He noted occasional anginal pain on exertion and rare episodes of palpitation not related to emotion or to any specific activity.

Physical examination. Blood pressure was 180/100 mm. Hg, pulse 100 per minute and regular, and respirations 18 per minute. The positive physical findings included mild respiratory distress, cervical venous distention in the upright position, and bilateral basilar respiratory râles. The cardiac apex beat was beyond the mid-clavicular line. The rhythm was regular, with a protodiastolic gallop. The liver was enlarged 3 cm. below the right costal margin, and slight ankle edema was present.

Laboratory data. Blood count, routine blood chemistry, and urine analysis were normal. The SGOT was 9 units, and LDH was 415. VDRL was negative. The chest x-ray film showed left ventricular enlargement and moderate pulmonary venous congestion. The ECG on admission showed striking changes in the QRS complex when compared to electrocardiograms taken previously (Fig. 1,*B*). Positive deflections with an initially slurred component were now present in Leads I and AVL and in all precordial leads. Entirely negative deflections with initial slurring were present in Leads II, III, and AVF. The P-R interval remained 0.22 second, and the QRS duration lengthened to 0.16 second.

Hospital course. Treatment consisted of bed rest, digitalis, low-sodium diet, and parenteral mercurial

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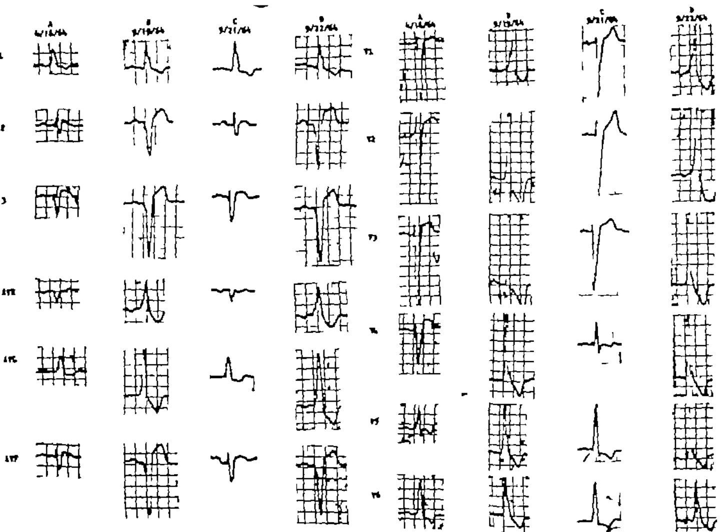


Fig. 1. *A*, Preadmission ECG showing complete LBBB. Small q waves and S-T segment characteristic of injury current in Leads II, III, and AVF suggest old inferoseptal damage. *B*, Admission ECG showing entirely positive deflections in Leads I and AVL and in all precordial leads. Negative deflections are present in Leads II, III, and AVF. All complexes begin with an initial slurring. *C*, Reversion to preadmission pattern of LBBB on third hospital day. *D*, Reappearance of WPW LBBB pattern on fourth hospital day.



Fig 2A Horizontal plane. The QRS loop is predominantly oriented to the left and anteriorly and is inscribed counterclockwise. The entire efferent limb shows conduction delay that is most pronounced initially. Mid and terminal slurring is present and the latter is inscribed clockwise toward the left-posterior quadrant. Time marking is at 2.5-msec. intervals.

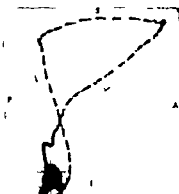


Fig 2B Right sagittal plane. The QRS loop is oriented superiorly and anteriorly with a predominantly counterclockwise inscription. The delta vector is directed superiorly.



Fig 2C Frontal plane. The QRS loop is inscribed counterclockwise and is directed superiorly and leftward. The entire efferent limb shows a conduction delay most marked initially and is directed to the left and superiorly.

diuretics. No clinical or laboratory evidence for acute myocardial damage was demonstrated. On the third hospital day (Sept. 21 1964) an ECG showed reversion to the preadmission pattern of left bundle branch block (LBBB) (Fig. 1 C). On the following day the ECG pattern of combined Wolff Parkinson-White syndrome (WPW) and LBBB reappeared (Fig 1,D). The vectorcardiogram (Frank system) was taken on the fourth hospital day (Fig 2). Visits to the clinic up to 10 months after discharge have showed persistence of pre-excitation and LBBB on the ECG.

Discussion

The vectorcardiographic diagnosis of the Wolff Parkinson-White (WPW) syndrome depends on the presence of an initial conduction delay of varying duration that corresponds to the delta vector of the QRS loop. In the above-described case the predominant portion of the delta vector projected anteriorly and slightly leftward in the horizontal plane. In the electrocardiogram this anomalous vector was recorded as an upright deflection in both the right and left precordial leads, a pattern which from the point of view of morphology corresponds to Type A WPW initially described by Rosenbaum and associates.[5,6] In this type most writers agree that premature ventricular activation probably occurs initially in the posterobasal or basilar septal area of the left ventricle, with electrical propagation in a posteroanterior direction.[7,8]

The initial conduction delay in the above mentioned case involved the entire efferent limb of the QRS loop which is in accord with the findings of Masse and associates who described a longer duration of the delta wave in Type A than in Type B pre-excitation. After the initial delay in inscription the remainder of ventricular activation was aberrantly inscribed with further conduction delay in the mid and terminal portions of the QRS loop. Terminal slowing was most pronounced in the horizontal plane and predominantly directed in a clockwise manner into the left-posterior quadrant. The electrical forces responsible for this

terminal conduction disorder were most likely influenced by a block of the left bundle. The last areas to be depolarized in LBBB include the upper left septum and free left ventricular wall with forces directed to the left posteriorly and superiorly.[10] Peri-infarction block, left ventricular hypertrophy, and LBBB complicated by infarction may similarly alter the terminal QRS forces. In LBBB complicated by infarction of the left ventricular free wall, however, the terminal vector forces are more disposed to the right and posteriorly. In LBBB associated with diffuse interventricular septal damage due to infarction or fibrosis, the initial forces are usually directed to the right and anteriorly. Uncomplicated LBBB is the most likely possibility, therefore, and, in addition, this block was present for years before the appearance of the pre-excitation.

Initial septal activation from right to left, which is usual in LBBB, was entirely obscured in this case by pre-excitation of the left posterior myocardium with subsequent myocardial spread in a postero-anterior direction removed from the normal conduction pathways.

In this VCG, pre-excitation forces directed to the left anteriorly and markedly superiorly dominated the entire efferent limb of the QRS loop for approximately 60 msec., although the most pronounced slurring involved the initial 15 to 20 msec.

Further evidence of the predominance of pre-excitation in the development of ventricular depolarization was manifested by the direction of the repolarization forces. The ST and T vectors directed posteriorly, inferiorly, and slightly to the right behave in accordance with and secondary to the delta vector of pre-excitation rather than to the vectors of the coexistent LBBB.

With the appearance of pre-excitation the P-R interval was unchanged, so that prolonged A-V conduction time of 0.22 second remained. Pick, discussing prolonged P-R intervals in WPW, postulated an anomalous pathway within or below the A-V node.[1] Premature activation of a portion of the myocardium removed from the normal conducting pathways was considered to be delayed because of a concomitant block of the sinus impulse in that portion of the A-V node or common bundle before the accessory pathway was entered. Although a short P-R interval is usual, it is not crucial to the diagnosis of pre-excitation. In 12.5 per cent of the 40 cases presented by Massie and associates,[9] the P-R interval was 0.13 second or more, with those of Type A usually having longer P-R intervals than those of Type B.

Summary

A case demonstrating coexistent ipsilateral ventricular pre-excitation and left bundle branch block with delayed atrioventricular conduction is presented. The VCG and ECG features are discussed.

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Anomalous origins of pulmonary arteries from pulmonary trunk ("crossed pulmonary arteries")

Observation in a case with 18 trisomy syndrome

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The major pulmonary arteries only uncommonly are anomalous. If an anomaly is present, it may take one of several forms, including stenosis, absence, or aberrant site of origin.

The purpose of this communication is to report a case of aberrant pulmonary arteries of a type which, in so far as we are aware, has not previously been reported. The essential feature of the anomaly was that the left pulmonary artery originated to the right of the right pulmonary artery. In this way, the two pulmonary arteries crossed each other as they coursed to their respective lungs. Knowledge of the occurrence of this anomaly may aid in the interpretation of angiocardiograms in the understanding of an unusual course of the pulmonary arteries as during surgical exposure of the mediastinum.

Report of case

The patient, a female infant who weighed 5 pounds at birth, was referred to the University of Minnesota Hospitals when 12 days of age for evaluation of a lumbosacral myelomeningocele and bilateral equinovarus deformity of the feet. Neurological examination revealed signs of involvement of the spinal cord below the level of T_{10}. The additional abnormal findings included micrognathia, small palpebral fissures, high arched palate, low-set malformed ears, limited adduction of the hips, and bilateral overlapping of third and fourth fingers by the index and little fingers. The general picture suggested the 18 trisomy syndrome.[1-3] Chromosomal studies from leukocyte cultures revealed an 18 trisomy of the nondysjunction type. The patient exhibited repeated episodes of apnea, which responded to resuscitative measures. On the sixth hospital day, however, death occurred.

At necropsy, in addition to the externally evident anomalies mentioned, the Arnold-Chiari malformation, bilateral hydroureter and hydronephrosis, partial malrotation of the intestine, and cardiovascular anomalies to be described were found. Each lung contained two lobes.

The cardiovascular system exhibited a persistent left superior vena cava which joined the coronary sinus and, additionally, two anomalous complexes. One of the latter involved the pulmonary arteries and is the subject of this report; the other was represented by an atrial septal defect lying superiorly to the fossa ovalis associated with anomalous connection to the right atrium of the two pulmonary veins from the upper lobe of the right lung (Fig. 1). The aorta and pulmonary trunk arose normally and bore normal external relationships to each other. From the exterior, a patent ductus arteriosus occupied a normal position between the left upper angle of the pulmonary trunk and the aorta (Fig. 2, a, b, and).

Examination of the interior of the pulmonary

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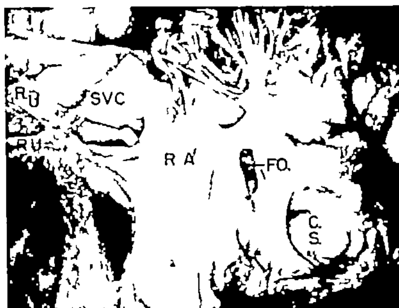


Fig. 1. Interior of right atrium (R. A.). Above the foramen ovale (F.O.), which is patent, is a defect (*containing probe*) in the atrial septum. This lies near the entrance of the superior vena cava (S.V.C.). Two pulmonary veins (R.U.) from the upper lobe of the right lung join the right atrium anomalously. The other pulmonary veins joined the left atrium in normal fashion.

trunk revealed the fact that the sites of origin of the left and right pulmonary arteries were anomalous. The ostia of these arteries were in the posterior wall of the pulmonary trunk; the ostium of the left pulmonary artery lay to the right and superiorly to that of the right pulmonary artery (Fig. 2, *d*). The ostium of the left pulmonary artery lay posteriorly to the anticipated location of the ostium of a normal right pulmonary artery, whereas the ostium of the right pulmonary artery lay inferiorly to the anticipated site of the ostium of a normal left pulmonary artery.

The pulmonary ostium of the ductus arteriosus lay superiorly and to the left of the ostium of the left pulmonary artery, the two ostia being closely allied and distinct from one another.

From the anomalous position of origin, each pulmonary artery proceeded to its respective lung to course anteriorly to the tracheal bifurcation. In view of the position of the ostia and the course of the two pulmonary arteries these vessels crossed one another, the left lying anteriorly to the right of the right pulmonary artery (Fig. 2, *b* and *c*). After the two pulmonary arteries crossed each other, the left pulmonary artery lay more superiorly than did the right.

Comment

In a review of the pathologic aspects of the 18 trisomy syndrome Lewis[2] found a high incidence of associated cardiac malformations, the most common ones being ventricular septal defect, patent ductus arteriosus, and bicuspid aortic and pulmonary valves. Cardiac malformations less commonly described in the 18 trisomy syndrome and usually associated with a ventricular septal defect were: (1) mitral atresia with hypoplastic left ventricle and aorta,[2] (2) endocardial fibroelastosis,[3] (3) coarctation of the aorta,[3,4] (4) complete transposition of the great vessels,[4] (5) persistent common atrioventricular canal,[5] (6) persistent left superior vena cava,[5] (7) origin of both great vessels from the right ventricle,[6] (8) tetralogy of Fallot,[7] (9) ventricular septal defect associated with pulmonary valvular stenosis,[8,9] (10) idiopathic hypertrophy of the ventricular septum,[8] (11) mitral stenosis,[9,10] (12) atrial septal defect at the fossa ovalis,[11] (13) cor triloculare,[12] (14) mild aortic stenosis,[13] (15) redundancy and/or abnormality of cuspid tissue of either the atrioventricular or semilunar valves,[8,9,11,13-16] (16) dextroposed aorta overriding ventricular septal defect,[9,10,16] and (17) shallow aneurysm of ascending aorta.[16]

A recognized form of anomalous pulmonary arterial origin is that in which the left pulmonary artery arises from the right pulmonary artery. It then passes pos-

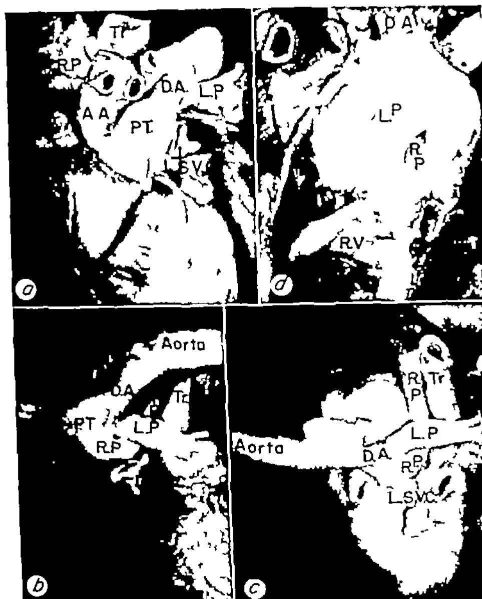


Fig. 2. a, The heart and great vessels from in front. The ascending aorta (*A A*) and the pulmonary trunk (*P T*) are normally related to each other. The course of the ductus arteriosus (*D A*) is in a normal position. The left pulmonary artery (*L P*) in this perspective is seen only in part because of its anomalous origin, to be shown in other illustrations. The left superior vena cava (*L S V C*) is persistent and communicates with the coronary sinus. *R P*, Right pulmonary artery as it joins the right lung. *T*, Trachea. *b,* The heart and great vessels viewed from the left side. Extending from the pulmonary trunk (*P T*) to the descending aorta is the normally positioned ductus arteriosus (*D A*). The left pulmonary artery (*L P*), which arises from the right posterior aspect of the pulmonary trunk, is seen crossing anteriorly to the right pulmonary artery (*R P*); the latter vessel arises from the left posterior aspect of the pulmonary trunk. *T*, Trachea. *L S V C*, Left superior vena cava. *c,* The heart and great vessels viewed from the left side. The descending aorta and the ductus arteriosus (*D A*) have been retracted anteriorly to expose the two pulmonary arteries. The ostium of the left pulmonary artery (*L P*) arises from the right aspect of the pulmonary trunk near the origin of the ductus arteriosus, whereas the right pulmonary artery (*R P*) arises from the left side of the posterior aspect of the pulmonary trunk. The two pulmonary arteries cross in front of the bifurcation of the trachea (*T*). *d,* Interior of the pulmonary trunk. The ostium of the left pulmonary artery (*L P*) lies toward the right and superiorly to the ostium of the right pulmonary artery (*R P*). The pulmonary ostium of the ductus arteriosus (*D A*) is independent from that of the left pulmonary artery.

teriorly to the right main bronchus and trachea and ultimately reaches the left lung. An explanation for this anomaly is that the true left pulmonary artery either fails to form or does not fully develop and that the anomalous left pulmonary artery in essence is a collateral vessel arising from the right pulmonary artery. In a discussion of this entity[17] we have suggested that although in all of the reported cases of anomalous origin of the left pulmonary artery from the right pulmonary artery the anomalous vessel passes posteriorly to the trachea, it is theoretically possible that an anomalous left pulmonary artery could pass anteriorly to the trachea.

In dealing with the current case, we considered the possibility that the crossing of the pulmonary arteries might represent a situation in which the left pulmonary artery arose from the right but passed anteriorly to the trachea as had been postulated. Anatomically, however, it is evident that the two pulmonary arteries arise independently from each other and each in turn arises from the pulmonary trunk. Therefore some other explanation of the developmental basis of the anomalous position of the two pulmonary arterial ostia must be entertained. At the moment we do not have a ready explanation but one possibility may be considered. If one refers to the gross specimen, it is envisioned that by starting with normal origins of the two pulmonary arteries and by rotating them in a counterclockwise direction, one could reach a point at which the ostia of the two pulmonary arteries and the relationship of the ductus arteriosus to the left pulmonary artery would be as observed in our case (Fig. 3). This brings up for consideration the possibility that the fundamental origin of the two pulmonary arteries had been normal but that the anomaly as now viewed was derived from faulty differential growth within the pulmonary trunk itself. Such a process could cause a distortion in the position of the two pulmonary arterial ostia which originally had been in a normal position.

Congdon[18] has emphasized the fact that the distance between the origin of the two pulmonary vessels remains nearly constant during the earlier postbranchial phase.

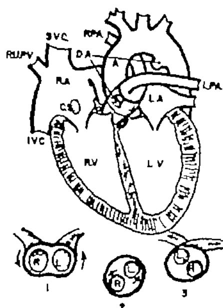


Fig. 3. *Upper.* Diagrammatic representation of anomalous origin of the pulmonary arteries from pulmonary trunk. Left pulmonary artery (*L.P.A.*) arises to the right of and superior to the right pulmonary artery (*R.P.A.*). The two pulmonary arteries cross as they proceed to their respective lungs. *The patent ductus arteriosus (D.A.) connects* normally with the pulmonary trunk and aorta (*A*). The pulmonary veins of the upper lobe of the right lung (*R.U.P.V.*) connect anomalously with the right atrium (*R.A.*). A defect of the atrial septum superior and posterior to the fossa ovalis is present. *I.V.C.*, Inferior vena cava. *S.V.C.*, Superior vena cava. Persistent left superior vena cava which connected with the coronary sinus (*C.S.*) is not shown. *Lower.* Diagrammatic representation of developmental explanation of the anomalous origin of the pulmonary arteries. *It is envisioned that, if the* normal relationship of the orifices of the pulmonary arteries (*1*) is rotated 120 degrees in a counterclockwise direction (*2*), the relationship of the pulmonary orifices as observed in this case will be obtained (*3*). *R*, Orifice of right pulmonary artery. *L*, Orifice of left pulmonary artery.

In contrast, during the period of rapid descent of the heart and great vessels the origins of the two pulmonary vessels approach each other and are almost joined. The process which brings the pulmonary arterial origins near each other is one of torsion of the pulmonary stem and fusion of the walls of the pulmonary arches with elongation of the pulmonary trunk as postulated by Bremer.[19] Movement of one or both pulmonary vessels through the substance of the wall of the pulmonary stem is postulated by Congdon. It appears

to be possible that either abnormal torsion and rotation of the pulmonary trunk or migration of the origin of the pulmonary vessels could occur at this stage to yield the malformation of the pulmonary arteries under discussion.

The phenomenon of crossing of the two pulmonary arteries in our case is derived fundamentally from the fact that the ostia of the two vessels were malpositioned one with respect to the other. There is another entity known to us in which the two pulmonary arterial branches cross each other. This was represented by a case included in the monograph of Stewart, Kincaid and Edwards.[15] In that case the right pulmonary artery arose from the pulmonary trunk in a normal position whereas the left pulmonary artery arose from the anterior aspect of the ascending aorta. As each artery coursed to its respective lung the two crossed each other and, as in the case herein reported, the left pulmonary artery was more anterior to the right at the point of crossing.

Although the process involving the pulmonary arteries in the case presented is rare, it deserves a name. We suggest, therefore, that it be called "crossed pulmonary arteries."

It becomes immediately apparent that there are two types of *crossed pulmonary arteries*. The first is represented by the case herein reported in which the two arteries arise from the pulmonary trunk and in this way the anomaly yields no disturbance of the circulation. The second type of *crossed pulmonary arteries*, that described by Stewart and associates, is expected to be functionally significant since in this type one of the pulmonary arteries arises from the aorta.

Summary

The case of a newborn infant with the 18 trisomy syndrome having the characteristic external features of micrognathia, small palpebral fissures, high arched palate, low-set malformed ears, limited adduction of hips, and bilateral overlapping of the third and fourth fingers by the index and little fingers is presented. There were two significant cardiovascular malformations. The first was represented by an atrial septal defect lying superiorly to the fossa ovalis associated with anomalous connection of the right upper pulmonary veins to the right atrium.

The second anomaly, which is the basis for this report, was represented by malposition of the origins of the two pulmonary arteries from the pulmonary trunk, in that the left pulmonary arterial ostium lay to the right of and somewhat superior to the ostium of the right pulmonary artery. From the anomalous site of origin each pulmonary artery coursed to its respective lung and in this course the two vessels crossed each other. It is suggested that the condition be called "crossed pulmonary arteries." The developmental explanation for the malposition of the ostia of the two pulmonary arteries is not certain, but it is suggested that the phenomenon may result from faulty differential growth within the pulmonary trunk causing the two branches to lose normal relationships with respect to each other.

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Calcification of the aorta and main vessels in rheumatoid arthritis

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Rheumatoid arthritis is being increasingly recognized as a systemic disease process which affects not only the joints and subcutaneous tissues but also the nervous system muscles, lungs, and cardiovascular system Although a myocarditis and pericarditis and even endocarditis have been frequently described[1] there have been only a few reports of involvement of the aorta in rheumatoid arthritis.[2,3] However in none of these was calcification of the aorta associated Therefore we now present what we believe to be the first report of a case of calcification of the aorta and its main branches associated with rheumatoid arthritis.

Case report

\ \ an 18-year-old male, a farmer by occupation was admitted to the Unit of the Professor of Medicine General Hospital, Colombo, on Feb 16, 1965 because of a 2-year-history of intermittent pain and swelling of the large joints The condition had commenced in the left a kle and then spread to the knees and the left wrist I addition, there had been pain in the left metacarpophalangeal and proximal interphalangeal joi ts. A mild fever had accompanied these. The pa and stiffness had been worse in the mornings The swelling had gradually subsided over a period of month leaving only some residual pain i the left knee. About a year later he had developed pain and tenderness over the right heel and tendo Achillis, and 3 months later pain and swelling of both knees, the left ankle and both hips. The latter condition had persisted since then Subsequently he developed pain in the right ankle both wrists, and both sacroiliac joints. He had had no breathlessness, faintness, headaches, visual disturbances or claudication in the arms or jaws.

Previous history He had been born at term and had been free of any illness until 8 years of age when he had developed fever vomiting, and generalized swelling of the body a few days after a thorn-prick.

Since then he had been in good health until the present illness. There was no history of exposure to venereal disease.

Family history His mother who had died in childbirth 13 years ago at about 45 years of age had been treated for stiffness of the knee joints from the age of 35 years, but no further information in regard to this illness was vailable

Examination The patient (Fig 1) wa a poorly nourished male 59½ inches tall, nd weighing 70 pounds He had moderate clubbing of the fingers but not of the toes There was tenderness and swelling of the left knee with a slight flexion deformity The right knee was swollen, tender and had a effusion Both ankles and tendo Achillis were tender Tenderness on the wrists and sacroiliac joints ppeared later during his stay i the hospital Crepitus was elicited in the metacarpophalangeal and proximal interphalangeal joi ts but there was deformity of these. There was no limitation of movement of the spine. The quadriceps were markedly wasted. \ nodules were palpable. Examination of the cardiovascular system revealed feeble left radial pulse and a diminished left carotid pulse The blood pressures were 115/50 mm. Hg in the right arm 95/70 in the left arm, nd 115/50 m the lower limbs A systolic thrill was felt over the left carotid artery and a systolic murmur was udible in the aortic area and in both sides of the neck being maximal in the left side. There was no diastolic murmur and the heart was not enlarged

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Fig 1 The patient Swelling of the knee joints and marked wasting of the quadriceps are seen.

The other systems were quite normal. The optic fundi showed no atrophy and the fields of vision were full

Investigations The Mantoux test was negative. No reducing substance was found in the urine and the ferric chloride test for homogentisic acid was negative The results of other laboratory investigations were as follows V D R.L. nonreactive Wassermann reaction negative Reiter protein complement fixation test negative; Latex fixation test repeatedly negative antistreptolysin titer 300 Todd units, erythrocyte sedimentation rate 131 mm in the first hour (Westergren) WBC 20,800 with 66 per cent neutrophils 28 per cent lymphocytes, 3 per cent eosinophils, and 3 per cent monocytes; preparations for L.E cells repeatedly negative blood urea 42 mg per cent, serum calcium 8 7 mg per cent, serum alkaline phosphatase 11 King Armstrong units, serum cholesterol 181 mg per cent SGOT 14 Fraenkel units, bleeding time 3½ minutes, clotting time 2 minutes. The liver function tests were normal The serum protein was 7.3 Gm. per 100 ml with albumin 3 3 Gm. and globulin 4 0 Gm A synovial biopsy was done and the histologic appearances were reported as being suggestive of rheumatoid arthritis The electrocardiographic examination showed some degree of intraventricular block (Fig 2).

Radiologic examination There was narrowing of the joint space and erosion of the bone especially in the left knee and marked osteoporosis around the joints (Figs. 3 and 4) X-ray films of the sacroiliac joints and spine were quite normal An x-ray film of the hands and wrists showed no abnormality A teleradiogram of the chest and a left lateral view

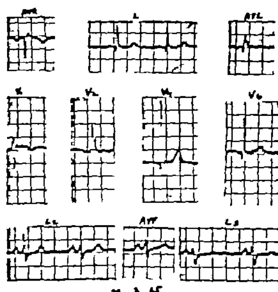


Fig 2 Electrocardiogram RSR pattern in chest Lead V₁ with widening of complex, suggesting some degree of intraventricular block



Fig 3 Anteroposterior x-ray film of the knee joint showing narrowing of the joint space which is more marked in the left.

showed calcification of the aorta all the way down to the diaphragm (Figs. 5 and 6). Calcification of the aorta with dilatation and calcification of the main vessels of the neck were seen in a left anterior oblique view (Fig. 7), which superficially appeared to suggest a film taken during angiocardiography.

Discussion

This patient presented with a chronic polyarthritis and extensive calcification of the aorta. The association of morning stiffness, pain and tenderness and swelling of more than one joint and the simultaneous involvement of the knee joints, together with the radiologic appearances of the knee joints and the histologic appearances of the synovium appear to satisfy the criteria required for the diagnosis of rheumatoid arthritis.[4] In rheumatoid arthritis, the large joints may be involved first as often as are the small joints. The onset of arthritis in this patient when he was 16 years old precluded the diagnosis of juvenile rheumatoid arthritis.[6] However, the age limit of 15 years for the onset of juvenile rheumatoid arthritis is an arbitrary criterion and the monoarticular onset and absence of a positive latex fixation test are common in that group.[7,8]

Ankylosing spondylitis may present with a peripheral polyarthritis, and the histo-

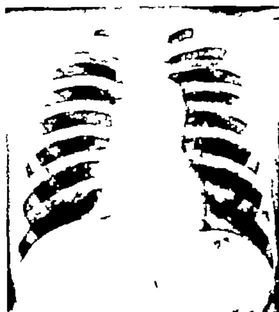


Fig. 5. Teleradiogram showing widening of the aorta with calcification.



Fig. 4. Lateral view x-ray film of the left knee, showing marked osteoporosis.



Fig. 6. Left lateral view x-ray film showing calcification of the arch and descending aorta as far as the diaphragm.



Fig. 7. Left anterior oblique sella x-ray film. Calcification of the aorta and branches of the arch are clearly seen.

logic appearance of the synovium may be that typical of rheumatoid arthritis.[8] In the absence of any radiologic changes in the sacroiliac joints, we considered ankylosing spondylitis to be less likely despite the tenderness over these joints. Sacroiliac arthritis may occur in classic rheumatoid arthritis but rarely shows ankylosis.[10] However, there are cases on record in which the changes typical of ankylosing spondylitis have appeared 5 years after the onset of peripheral arthritis[11] and patients with probable juvenile rheumatoid arthritis are also known to subsequently develop ankylosing spondylitis.[8] Involvement of the aorta is known to occur in ankylosing spondylitis. In most of these cases, thickening of the aortic intima spreads for not more than a few centimeters into the ascending aorta[12] but a case has been reported in which a hyaline thickening extended down to the level of the renal arteries.[11] Calcification occurring as a sequel to a similar process cannot be excluded in our patient.

The occurrence of disease of the aorta in association with rheumatoid arthritis has received but scant attention until of late. Studies of the pathologic changes in the cardiovascular system revealed granulomata and thickening of the endocardium which sometimes extended to involve the aortic valve cusps, even with calcification of the aortic valve.[1] It is possible that a similar process may extend to involve the entire aorta. However, recently the association of Takayasu's arteritis with rheumatoid arthritis has been described.[2,3] In many other reports of Takayasu's arteritis the occurrence of arthralgia or a transient polyarthritis has been noted.[13] A chronic polyarthritis had been associated in one case in another series.[14]

The striking feature in our patient was the extensive calcification easily visible on radiologic examination. Calcification of the aorta is a well known feature of atherosclerosis, in which case it usually affects the arch, and of syphilis, in which case it affects mainly the ascending aorta. Sometimes it may extend beyond this.[15] Syphilis has been excluded in our patient by the absence of a history of exposure and by negative serologic tests. Extensive calcification of the aorta has been also reported in alkaptonuria.[16] It may also occur in Takayasu's arteritis[17,18] and in the middle aortic syndrome,[19] which is probably the same pathologic process occurring more distally. However, no particular emphasis has been laid on this or on its radiologic detection. In one case report[18] calcification of the entire ascending aorta, arch, and descending aorta was noted as a radiologic finding. In most other reports it was described as a finding either at autopsy or at surgical exploration. Thus, in Case 1 described by Lessof and Glynn,[17] heavy calcification was found at autopsy with no mention having been made of this as a radiologic finding here or in an earlier description of the same case.[20] Calcification has been commented on as being not a usual feature of Takayasu's arteritis, occurring only if the patient survives sufficiently long.[14] The extensive involvement of the aorta in our patient makes the diagnosis of Takayasu's arteritis possible.

For a diagnosis of Takayasu's arteritis in the living aortography is considered by some to be necessary,[21,22] although it has not been performed in many reported cases. Unfortunately facilities for this investigative procedure in this case were not available. The occurrence of a diminished pulse in one arm and in the carotid artery and the exclusion of syphilis makes likely the diagnosis of "obliterative aortic disease" i.e. of Takayasu's arteritis.

The occurrence of the disease in a male, the occurrence of extensive calcification and the association with rheumatoid arthritis *must make this case a rare one.*

Summary

A case of extensive aortic calcification associated with rheumatoid arthritis is presented. The features of this case were (1) evidence of a diffuse aortitis involving the ascending aorta, arch and descending aorta associated with rheumatoid arthritis and (2) calcification of the aorta, as clearly demonstrated by radiologic examination.

The evidence for the diagnosis of rheumatoid arthritis is discussed but ankylosing spondylitis could not be excluded altogether.

Although calcification as a sequel to Takayasu's type of arteritis is considered to be likely we were unable to draw any definite conclusions in the absence of any histopathologic examinations.

A true rheumatoid process involving the aorta cannot be excluded either.

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Clinical pathologic conference

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Clinical history

A 54-year-old Negro man was admitted to the Medical College of Virginia on Jan. 12, 1964, with a chief complaint of "swelling and chest pain." The chest pain was described as a burning sensation substernally which occurred immediately after eating. The pain was aggravated by lying down and was most pronounced at night. It was relieved by the ingestion of soda or by the upright position. He denied hematemesis, melena, eructation, constipation, diarrhea, or jaundice. He had noticed increasing shortness of breath, 3-pillow orthopnea, paroxysmal nocturnal dyspnea, and marked swelling of his feet and legs for approximately 6 weeks prior to admission.

He had been hospitalized at the Medical College of Virginia in 1953 because of shortness of breath, dyspnea, orthopnea, and swelling of his ankles. He denied any symptoms prior to this admission. There was no history of rheumatic fever. Physical examination revealed râles in both lungs, signs of left pleural effusion, and distention of the neck veins. The cardiac apical impulse was in the anterior axillary line in the sixth left intercostal space. There was a faint apical mid-diastolic rumble, with a loud first heart sound and a Grade 2 apical pansystolic murmur. An electrocardiogram on admission revealed atrial fibrillation with a rate of 1 0. The electrocardiogram 4 days later (Fig. 1) revealed atrial flutter with a varying 2:1 or 3:1 block. An x-ray film of the chest (Fig. 2) showed left ventricular and probable left atrial enlargement and prominent hilar markings. He was thought to have mitral stenosis. He was treated with digitalis and a low-salt diet. He returned in June 1955 complaining of shortness of breath and swelling of his ankles. He was treated with digitalis and diuretics and did fairly well. Fluoroscopy in 1956 showed no unusual hilar pulsation. He remained in a reasonably good state of health, able to climb one flight of steps without severe dyspnea, and was generally free of edema until late 1963.

He had had sporadic syncopal attacks since 1962 which were characterized by dizziness and then unconsciousness, the latter lasting from 10 to 15 minutes. He would occasionally have epileptiform movements while unconscious, and the spells of unconsciousness were followed by a dull aching headache, lethargy, and sluggishness.

Past medical history revealed that he had been treated for syphilis in 1945 but in February, 1962, the serologic test for syphilis was noted to be positive again. He was treated in the outpatient department with 7.2 million units of Bicillin over a 3-week period. The serology was reported to be negative in August, 1962. Family history revealed that his father had died of heart disease, and that his mother had died with coronary thrombosis. One sibling died with a "leaking heart." Social history was unremarkable except for the heavy consumption of alcohol on weekends.

Physical examination. The blood pressure was 100/60 mm. Hg (both arms), pulse 80, respirations 20, and temperature 98.6°F. The patient was a somewhat lethargic, cyanotic, middle-aged Negro man in mild respiratory distress, with marked edema of the lower extremities. The pupils were small and reacted sluggishly to light but normally to accommodation. Funduscopic examination showed increased tortuosity of the retinal arterioles and a slight degree of A-V nicking. The neck was supple. The neck veins were distended even with the patient upright. Carotid pulsations were equal bilaterally. The chest showed an increase in the anteroposterior diameter with increased resonance over both lung fields. The diaphragms were low. Coarse scattered râles were noted in the left lung base posteriorly, and there was a diffuse expiratory wheezing with a prolongation of the expiratory phase. There was retraction of the lower intercostal

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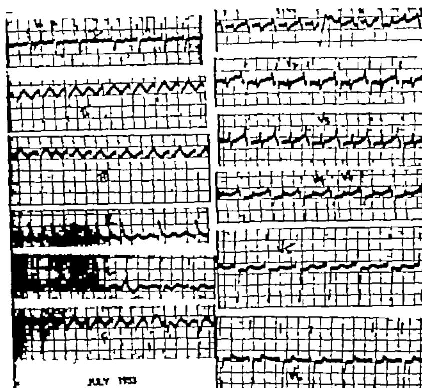


Fig. 1. Electrocardiogram demonstrates atrial flutter, superiorly oriented mean frontal QRS vector and right ventricular hypertrophy.



Fig. 2. X-ray film (1953) demonstrates left ventricular enlargement and prominent pulmonary vasculature.

spaces bilaterally during inspiration. The apical impulse was prominent and located in the sixth intercostal space at the anterior axillary line. There was a prominent left parasternal lift. The rhythm was grossly irregular. The mitral first sound was decreased and an opening snap was present. There was a soft pansystolic apical murmur without respiratory variation. A diastolic rumble was heard after the opening snap and ended before the first sound. The abdomen was distended with shifting dullness in the flanks and edema of the skin. The edge of the liver was palpable 6 cm. below the right costal margin and was slightly tender. There was marked edema of the lower extremities. A hydrocele was present on the right side. Neurological examination was essentially negative.

Laboratory work. Hemoglobin was 14.2 Gm. per cent. WBC 6,250 with 61 per cent neutrophils, 6 per cent eosinophils, 1 per cent basophils, 31 per cent lymphocytes, and 4 per cent monocytes. The urine was acid, yellow, and cloudy with a specific gravity of 1.019. There was a trace of proteinuria but sugar and acetone were negative. Microscopic examination of the urine showed it to be loaded with white cells. The urine colony count showed *Proteus mirabilis* and the Klebsiella-Aerobacter group present in a concentration of less than 10,000 organisms per milliliter. Prothrombin concentration was 36 per cent. Blood urea nitrogen was 24 mg. per cent. Serum Na was 14 mEq./L., Cl 101

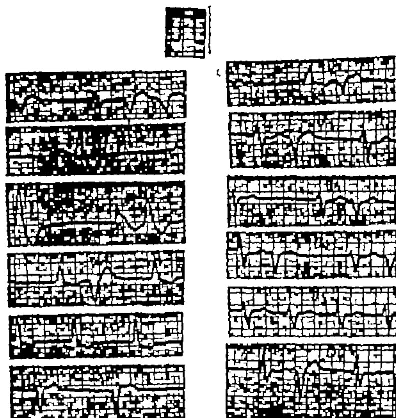


Fig. 3. Electrocardiogram (Jan. 12, 1965) demonstrates atrial fibrillation, right bundle branch block, and multiple ventricular ectopic beats.

mEq./L., K 3.8 mEq./L., CO₂ content 24 mEq./L., SGOT = 29 units. Serum bilirubin was 1.6 mg. per cent total with 0.8 mg. per cent direct. Sedimentation rate was 14. An electrocardiogram demonstrated atrial fibrillation, right bundle branch block, and multiple ventricular ectopic beats (Fig. 3). A chest film showed massive cardiomegaly with pulmonary vascular engorgement. Pericardial effusion could not be ruled out (Fig. 4).

The patient was treated with bed rest and vigorous diuresis. Digitalis was withheld and the patient lost 4 pounds. The serum electrolytes remained normal. The electrocardiogram was repeated and showed paroxysmal atrial tachycardia with varying degrees of A-V block. There were frequent ventricular ectopic beats and intermittent bigeminy. On the evening of Jan. 20, 1965, the patient vomited and fell out of bed. By the time he was seen by a physician no vital signs were present. An autopsy was obtained.

Clinical discussion

DR. RICHARDSON: The list of entities that can simulate rheumatic mitral stenosis is a long one. When atypical features are noted, it behooves the physician to use all potentially helpful means, including cardiac catheterization, angiocardiography, and fluoroscopy, to elucidate the anatomic diagnosis.

This patient presented abnormalities of several systems in addition to his heart. He came to the hospital because of substernal burning chest pain which occurred immediately after eating, was aggravated by lying down, was particularly pronounced at night, and was relieved by soda and by sitting up. These symptoms strongly suggest hiatus hernia, which is my first diagnosis. Secondly, he probably had syphilis. The protocol says that the patient had a positive serology on two occasions, and was treated with penicillin. In addition, his pupils did not respond to light but did respond to accommodation. To be sure about the Argyll Robertson pupil, one should have the additional description that the pupils were small and irregular and that they did not respond to mydriatics. In a middle-aged man with a positive serology and pupils of the sort



Fig. 4. X-ray film (January 1965) demonstrates massive cardiomegaly with pulmonary vascular engorgement.

described, my second diagnosis is late syphilis of the central nervous system.

The third diagnosis concerns the lungs. He had hyperresonance over the lower lung area, low diaphragms, wheezing with prolonged expiration, and retraction of the intercostal spaces with inspiration. Although the wheezing and prolonged expiration may be attributable to heart failure, the other signs suggest that he had emphysema.

The major problem centers around the heart. Could he have had syphilitic heart disease? I certainly do not think so. Syphilis affects the proximal ascending aorta and dilates it. This patient did not have a dilated aorta. Syphilis can affect the coronary artery ostia, but this patient had neither angina nor ECG evidence of coronary artery disease. Syphilis can produce aortic insufficiency, which this patient did not have. I must conclude that he did not have syphilitic heart disease. He had had neither rheumatic fever nor known heart trouble prior to the age of 42. Many patients with rheumatic heart disease do not have a history of rheumatic fever, and some cases of congenital heart disease may not be recognized prior to age 40, so that bit of past history is not of much help. At the age of 42 (in 1953) he came to this hospital with symptoms and signs of congestive heart failure. Physical examination showed that his cardiac apex was in the anterior-axillary line in the sixth left intercostal space. Although right ventricular enlargement can occasionally displace the apex leftward, it almost never displaces it downward. The finding of an apex impulse in the sixth intercostal space in the anterior-axillary line strongly suggests left ventricular enlargement. He had a mid-diastolic rumble, and an apical pansystolic murmur which was not very loud. There is no mention of clubbing or cyanosis.

In 1953 an electrocardiogram was recorded (Fig. 1). The rhythm is atrial flutter. The QRS complexes are very helpful. Note that the mean frontal plane vector is perpendicular to Lead I and points away from Leads II and III. The mean frontal plane vector points straight at the head, an unusual location that is strongly suggestive of several specific types of congenital heart disease. The only other type of heart disease that demonstrates this superiorly directed QRS vector is coronary disease with an inferior infarct, and there is no ECG evidence for this. In addition, there is a prominent R wave in Lead V_1 and a deep S in Lead V_6, which is quite compatible with right ventricular hypertrophy. There is slight slurring of the QRS in Lead V_1, which is not well seen in Lead V_1. This suggests a minor degree of conduction disturbance in the right ventricle. To repeat, the ECG shows marked left axis deviation, right ventricular hypertrophy, and absence of left ventricular hypertrophy.

An x-ray film obtained in 1953 (Fig. 2) gives exactly the opposite impression: the shape of the left lower heart border suggests left ventricular enlargement. The combination of right ventricular hypertrophy on the ECG and left ventricular enlargement on the x-ray film and physical examination suggests left heart disease plus marked pulmonary hypertension. I will return to this later.

The patient returned to the hospital in 1964 with the signs and symptoms of congestive heart failure. On physical examination he had distention of the neck veins, a big liver, and edema, all of which resulted from heart failure. In addition, he showed

proteinuria a total bilirubin of 1 6 mg per cent and a prothrombin concentration of 36 per cent In the presence of a big liver ascites and marked heart failure I would explain the mild hyperbilirubinemia and the hypoprothrombinemia on the basis of chronic passive congestion of the liver and the proteinuria by congestion of the kidneys. Heart failure does not explain an eosinophilia of 6 per cent or pyuria no good explanation for either is apparent

The apex beat was again described as being prominent in the sixth intercostal space in the anterior axillary line, once more suggesting left ventricular enlargement This point is of particular importance in excluding pure mitral stenosis. The block in mitral stenosis is upstream from the left ventricle and left ventricular enlargement should not occur in pure mitral stenosis. He had a right ventricular heave an opening snap and a diastolic murmur which is clearly described as mid-diastolic and ending before the first heart sound This is most likely the murmur of torrential flow into the left ventricle through the mitral valve and certainly not the usual murmur of mitral stenosis In mitral stenosis in which there is a marked elevation of left atrial pressure the diastolic rumble is usually heard completely through diastole even in the presence of atrial fibrillation Fibrillation may obscure the presystolic crescendo but it usually does not cause cessation of the murmur before the first heart sound A rumble that is short and mid-diastolic suggests an increased flow of blood through an open mitral valve rather than mitral stenosis. The soft apical pansystolic murmur which fails to vary with respiration suggests mild mitral insufficiency The intensity of the murmur as described leads me away from the diagnosis of mitral insufficiency as the primary cause of his enormous cardiomegaly Mitral insufficiency causing this man's heart disease ought to be obvious with a loud murmur The fact that the murmur did not vary with respiration is of some interest, since an increase in the loudness of a systolic murmur during inspiration suggests tricuspid insufficiency

The x-ray films are confusing In the first place he was not fluoroscoped The films show so much cardiomegaly that it is difficult to tell which chambers are enlarged although I would like to hear what Dr Baggerly thinks.

DR BAGGERLY The heart is huge in the posteroanterior view (Fig 4) There are four bulges of the left heart border which we interpreted as resulting from enlargement of the left atrial appendage and main pulmonary trunk between the left ventricle and aorta The pulmonary arteries are quite prominent in the hila On the films with barium in the esophagus, one sees that the esophagus was displaced to the right and in the lateral view it was displaced posteriorly The left main stem bronchus was elevated We can infer therefore that the left atrium is markedly enlarged and that pulmonary hypertension is present These findings strongly suggest a diagnosis of mitral insufficiency

DR. RICHARDSON I am not happy with a diagnosis of mitral insufficiency with such an insignificant systolic murmur The x ray findings are those of dilatation of the main pulmonary artery and marked dilatation of the pulmonary arterial branches. The patient probably has left ventricular enlargement but all cardiac chambers are enlarged and that is about as far as I can go

Some electrocardiograms were recorded on his last admission (Fig 3) He had marked prolongation of the QRS in Leads I and II consistent with a right bundle branch block and atrial fibrillation He still had marked left axis deviation The frontal plane axis was perpendicular to Lead I and away from Leads II III and aV_F He still had no ECG evidence of left ventricular enlargement

We can summarize our findings so far as follows He had heart disease that first produced symptoms in middle life He had a mid-diastolic rumble and a minimal systolic murmur His electrocardiogram showed a frontal plane mean QRS vector that pointed straight up at his head and associated right ventricular hypertrophy What are the possible diagnoses? Mitral stenosis is unlikely for the following reasons the murmur is quite short a large left ventricle is present and the frontal plane mean QRS vector points at his head Combined mitral stenosis and mitral insufficiency are also unlikely Although the ECG pattern and the heart size might occur in the case of combined mitral valvu

lar disease, the absence of a significant systolic murmur would be most unusual. Syphilitic heart disease can be excluded for the reasons that I have stated. There is no clinical or ECG evidence for arteriosclerotic heart disease. This leaves congenital heart disease, and certain rare forms of heart disease as possibilities. All diastolic rumbles are not due to mitral stenosis. An atrial septal defect may produce a diastolic rumble and the impression of an "opening snap" because of the presence of a widely split second sound, particularly when there is right bundle branch block. Tricuspid stenosis, of course, produces a rumble and an opening snap. Myxoma or sarcoma of the atrium can cause a rumble, and an opening snap which is called a "tumor plop." The "tumor plop" is supposed to be less snappy (i.e., more "ploppy") than the opening snap of mitral stenosis, but I have never heard a plop, so that I do not know.

The additional findings of fainting spells, convulsions, diastolic rumble, and sudden death suggest a ball valve thrombus or a left atrial myxoma. Ball valve thrombus occurs almost exclusively in rheumatic mitral disease. The duration of this man's disease is against either of these lesions. The lack of peripheral emboli is against a thrombus. None of these points absolutely rules out atrial thrombus or myxoma, however.

Aortic regurgitation produces an Austin Flint murmur which can simulate the murmur of mitral stenosis. We have no evidence for aortic valve disease. Ventricular septal defect and patent ductus arteriosus can each produce a torrential mid-diastolic rumble. Increased flow through the mitral valve, however, is associated with increased flow through a ventricular septal defect or patent ductus arteriosus. A loud systolic murmur or a continuous murmur would therefore be heard. This patient had neither. Active rheumatic fever is said to be accompanied occasionally by an apical rumble, the Carey Coombs murmur. Anemia can also cause a mid-diastolic rumble.

Since I do not believe that he had mitral stenosis or mitral insufficiency, the next most common cause of heart disease with very large pulmonary arteries in middle-aged people is atrial septal defect. I think that this patient had an atrial septal defect. Atrial septal defects can be divided into four classes. The first type occurs in the septum secundum, and is anatomically a defect in the mid portion of the atrium in the general region of the foramen ovale. A lesion that mimics it is partial anomalous drainage of the pulmonary veins into the right atrium. Frequently both lesions occur together. Both produce right axis deviation on the ECG. They are not associated with left axis deviation or the superiorly oriented mean QRS vector seen in this patient. I am convinced that the ECG pattern excludes a defect of the septum secundum with or without partial anomalous pulmonary venous drainage. Total anomalous pulmonary venous drainage would also be excluded on the same basis.

There are two kinds of atrial septal defects which do give superiorly oriented electrocardiographic vectors of the kind seen in this case. One is common atrium and the other is a septum primum defect. The latter is a defect low in the atrial septum that involves the valve rings, and at times, the upper ventricular septum as well. Both of these entities produce on the ECG a mean frontal QRS vector that points superiorly and also demonstrate right ventricular hypertrophy. Common atrium is usually associated with more cyanosis and is fatal in very early life. I was unable to find examples of patients with common atrium who survived to this age.

Septum primum defects are complicated embryologic and anatomic abnormalities which usually produce little cyanosis, and which may not seriously limit life. In addition, septum primum defects are usually associated with a cleft in the septal leaflet of the mitral valve leading to mitral regurgitation. The degree of left ventricular enlargement is closely related to the degree of mitral insufficiency. Pulmonary hypertension resulting from intimal proliferation and fibrosis and medial hypertrophy of the pulmonary arterioles occurs late in life in some cases of atrial septal defect. Our patient had left heart enlargement, ECG evidence of pulmonary hypertension, and a murmur suggestive of mitral regurgitation, and he lived to middle life. I shall make a diag-

septal defect of the primum type with cleft septal leaflet of the mitral valve left ventricular enlargement pulmonary vascular disease and pulmonary hypertension and cardiac failure.

In conclusion all that wheezes is not asthma and all that rumbles is not mitral stenosis. In atypical cases, all objective information that you can possibly obtain is desirable Cardiac catheterization and selective angiocardiography would have established a diagnosis, and possibly permitted an attempt at surgical cure

Clinical diagnosis (1) Rheumatic heart disease, with mitral stenosis and mitral insufficiency (2) Pulmonary emphysema. (3) Hiatus hernia.

Dr Richardson's diagnosis (1) Congenital heart disease atrial septal defect septum primum type. (2) Cleft mitral valve leaflet with mitral insufficiency (3) Cardiac failure with congestion of lungs, liver and extremities. (4) Pulmonary arteriolosclerosis, secondary to prolonged pulmonary hypertension (5) Hiatus hernia (6) Pulmonary emphysema (7) Syphilis of the central nervous system

Pathologic discussion

DR LURIE This patient died of congestive cardiac failure, as evidenced by the edema ascites, congestion of all the abdominal organs, marked congestion and edema of the lungs and dilatation of all the chambers of the heart There was also evidence at autopsy of previous episodes of cardiac decompensation as shown by the classic cardiac cirrhosis of the liver and interstitial fibrosis of the lungs with hemosiderin laden macrophages in the alveolar spaces.

Incidental findings included old foci of tuberculosis at the right apex and in the hilar lymph nodes Slight emphysema was present There was a moderate degree of atheromatosis of the aorta small healed renal infarcts, and small foci of chronic pyelonephritis. Unfortunately the autopsy protocol did not note whether there was a hiatus hernia There was no evidence of rheumatic fever or of syphilis on gross or microscopic examinations.

Now let us consider the main disease processes. The 800-gram heart practically filled the lower thorax. There was marked hypertrophy of both the right and left ventricles and of course, dilatation of all chambers The coronary vessels were remarkedly clear of atheroma. Looking from the right atrium into the left atrium (Fig 5) one could find but a wisp of tissue on the posterior-superior aspect representing the septum primum There was effectively



Fig 5 The view is from the right atrium into the left through the huge septal defect. The atria are enormously dilated. The remnant of the septum primum is the edge of the broad band on the left



Fig 6 View down upon the mitral valve shows the congenital cleft in the anterior leaflet. The dark area on the right is the opening of the tricuspid valve

one large common atrium In the left atrial appendage there was a small mural thrombus. The interventricular septum was intact. The pulmonary vessels and the superior and inferior venae cavae opened in their correct positions, and there was no transposition of vessels. There was a very definite cleft in the anterior leaflet of the mitral valve, which gave the appearance of three leaflets (Fig 6) The tricuspid valve was slightly anomalous in that the septal leaflet was rather short and tightly bound down by very short chordae tendineae to the septum. There was no fibrosis or thickening of any of these valves There was pulmonary arteriolosclerosis as Dr Richardson surmised there would be.

Now let us consider the classification of this lesion The defects of the atrial septum may be divided into two types (1) septum secundum type, and (2) septum primum or endocardial cushion type. The former are high in the atrial septum, separated from the atrioventricular groove by tissue and do not involve the A V valves. By contrast, the latter are low in the atrial septum extend down to the A V valves and are always associated with varying degrees of A V valve deformity In the case presented a large ostium primum defect existed associated with a cleft in the septal cusp of the mitral valve and short septal cusp and chordae tendineae of the tricuspid valve

This case raises two very interesting points. First, why had he had no symptoms or signs of heart disease until the age of 42 years? Secondly this man's father and sibling were reported to have died of heart disease. Is it possible that they also had congenital heart disease In the general population, the incidence of congenital heart disease is 2 to 3 per 1 000 births whereas the incidence among siblings is as high as 13 to 14 per 1 000 births. It is possible that there may have been a common teratogenic factor affecting the mother during pregnancy which was responsible for these congenital defects.

DR. MOON Wouldn't you have expected the man to be cyanotic? I realize that cyanosis may have been difficult to detect because of racial coloration but I would have thought that he would have been frankly cyanotic long before this, particularly with this degree of pulmonary vascular change I would also like to know whether you think that an operation would have helped him in this advanced stage of his disease?

DR. RICHARDSON It is easy to tell about cyanosis in Negro people if you suspect its presence you may easily obtain arterial blood and measure oxygen saturation.

Atrial septal defects cause cyanosis late in life The shunt is left to-right all during childhood and early adult life. It is only as obstructive pulmonary vascular disease develops in middle adult life that cyanosis occurs. Refractory heart failure and cyanosis have onset at about the same time, usually between 30 and 50 years of age in patients with atrial septal defect, and are closely correlated with the development of obstructive disease of the pulmonary arterioles Why the latter develops is uncertain. Probably prolonged torrential flow through the pulmonary artery gradually produces medial thicking and intimal proliferation and fibrosis. Severe elevation of pressure in the right heart occurs only when the pulmonary vascular lesions have become far advanced This elevation of right heart pressures favors right-to-left shunting of unoxygenated blood into the systemic circulation via the atrial defect and results in cyanosis.

As far as surgical correction goes I suspect that by the time of the final admission surgery would have been contraindicated The pulmonary vascular disease was probably irreversible In mitral stenosis and ventricular septal defect, pulmonary vascular disease frequently improves postoperatively This is far less likely with atrial septal defect. Another point against possible surgical benefit in this patient was the finding that the chordae tendineae bound down a leaflet of the tricuspid valve If this were a major lesion surgical correction would have been difficult

Final diagnoses (1) Congenital heart disease (a) atrial septal defect (endocardial cushion defect incomplete with cleft mitral valve minor defect of tricuspid valve (b) enlargement of both cardiac ventricles (c) atrial fibrillation (d) congestive heart failure (2) Pulmonary arteriolar disease medial hypertrophy and intimal proliferation and fibrosis (3 Pulmonary emph

Myocardial infarct and sudden coronary heart death in relation to coronary occlusion and collateral circulation

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The relationship between obliterating coronary diseases and pathologic changes in the myocardium and the significance of the coronary arterial anastomotic circulation and the definition of myocardial infarction are some of the basic still controversial and only partially answered problems in cardiovascular pathology today A thorough study of these problems should take into consideration the correlation of both the age and type of cardiac and coronary lesions, as well as the behavior of the anastomotic channels During the last 12 years such a study was performed in which two different methods were utilized resulting in significant findings which will be cited here in the discussion of these problems. (The results of this study were extensively reported in two previous papers.[1,2]) Two methods were employed which together with the material examined are now discussed

Injection plus corrosion study[1]

The method of injection of the coronary circulation by plastic substances to obtain vascular casts was selected for this study since it was thought that other proposed methods give only little information, particularly with regard to the arterial anastomotic circulation

The two plastic substances used were Geon Latex 576 and Neoprene 842A which are fluid at room temperature but solidify at temperatures in the range of 40 to 50°C with negligible shrinkage thus producing a true cast of the vessel lumen These substances were injected under a pressure ranging from 130 to 200 mm Hg through the aorta after air tight closure of the aortic valve. This was effected by use of an inserted rubber stopper held in place by an encircling ligature passing beneath the coronary arteries. Injection was aided by a slight rhythmical compression of the aortic bulb The latex was allowed to solidify and the myocardium then was fixed by immersion in 10 per cent formalin at 40 to 50°C for 48 to 72 hours, the exact period of time being commensurate with the size of the organ Before corrosion of the heart by concentrated hydrochloric acid solution several samplings of the myocardium were obtained for histologic study This was accomplished using a hollow cylinder 1 cm in diameter with a sharp cutting edge The arterial circulation including the extramural and intramural vessels and the intracardiac anastomotic system were studied in 79 selected normal hearts in 48 "pure (without coronary and myocardial lesions) hypertrophic hearts in 25 pure atrophic

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hearts, in 18 normal hearts of patients who died after chronic hypoxic diseases and in 217 hearts with coronary artery disease, taken from 147 patients who died in the hospital after chronic coronary cardiopathy and from 70 subjects who died a "sudden, unexpected death." Moreover the extracardiac anastomotic circulation in 23 hearts, the arterioluminal vessels in 48 hearts, and the venous circulation including the Thebesian vessels, in 86 hearts were studied with opportune modifications of the injection method

In this paper we are limiting the discussion of our findings to the arterial anastomotic circulation which although frequently investigated by various methods, continues to be a controversial problem. Uncertainties still remain with regard to the existence, distribution, and significance of the cardiac arterial anastomoses. Very recently Rodriguez and Robbins[3] concluded that intercoronary anastomoses probably exist in the normal adult heart, but that they are few and spotty in distribution Through the use of our injection method it was possible to calculate the frequency location and caliber of the collateral channels and to relate their modifications to the variations in the cardiac mass, to their presence in patients with histories of chronic hypoxic diseases (anemia, severe emphysema of the lungs, etc) and above all, to the grade of the stenosing processes of the coronary arteries and to the myocardial damage present.

The following general conclusion can be made with regard to our study of the cardiac collateral arterial circulation In all of the normal hearts examined an extensive intracardiac arterial anastomotic circulation was observed and two types of anastomotic channels were recognized (Figs. 1 3) (a) homocoronary anastomoses which connected branches of the same coronary artery and (b) intercoronary anastomoses



Fig. 1 Antero-right lateral surface of normal heart Septal anastomotic circulation *Arrow 1* Anterior descending branch, left coronary artery *Arrow 2* Marginal branch right coronary artery (Female 32 yr old.)



Fig. 2. Normal heart. Anterior surface. Intercoronary arterial anastomoses. *Arrow*: Anterior descending branch left coronary artery. (Male, 28 yr. old.)

which connected branches of the two or, when present, three (coronaria accessoria dextra or third coronary artery) coronary arteries.

With regard to the localization of these vessels, it can be said in brief that the collaterals are distributed throughout the entire thickness of the heart wall except for the immediate subepicardial tissue. The direction of the collateral branches is usually parallel or oblique with respect to the plane of the cardiac muscle bands, and these vessels often have a finely coiled appearance. Beneath the endocardium they form a very fine reticulum, whereas in the septum the main anastomotic channels appear as bundles of parallel branches, and in the atria as a large mesh-like vascular structure. With our method of vessel injection under pressure, the measured diameter of the vessel of the plastic cast must be considered to be the diameter of that vessel in maximum dilatation. With this in mind, the homocoronary anastomoses in the normal heart of an adult have a diameter ranging from 20 to 250 microns, whereas the intercoronary anastomoses range from 20 to 350 microns. Diameters of less than 20 microns probably exist but cannot be demonstrated with certainty in my material. In the hearts of the newborn infants the maximum intercoronary diameter recorded was about 50 microns. Because the collateral branches of both types occur in such large numbers, it is impossible to determine their exact number. However, in order to determine an approximate estimation of their frequency for comparison to the normal and diseased heart, it was decided to count all of the easily seen anastomotic vessels, i.e., those having a diameter of more than 100 to 150 microns. This was done for each individual heart, and the mean diameter of these vessels was likewise determined for each heart. This mean diameter



Fig 3 Normal heart. Homocoronary arterial anastomoses connecting secondary branches of the left coronary artery (Male 23 y old)

ranged from 150 to 280 microns in the normal adult heart with an average of 200 microns for the total number of normal hearts studied In the septum from 15 to 30 intercoronary anastomoses were counted with a diameter of 100 microns or more and an equal number was counted in the myocardial wall. The homocoronary anastomoses were far more numerous, averaging in the hundreds. In the right ventricle, where the wall is thinner than in the left, and where there is a relative reduction in vascularization when compared to the left the mean diameter of the homocoronary anastomoses was less and their frequency proportionally reduced. With respect to the distinction between the intercoronary and homocoronary anastomoses, it should be emphasized that this distinction must take into consideration the variation in distribution of the coronary arteries For example the septal anastomoses will be homocoronary when the posterior descending branch originates from the left coronary artery whereas, vice versa they will be intercoronary when the posterior descending branch is derived from the right coronary artery In summary it is possible to say that in normal human hearts any vascular area can communicate with an adjacent vascular area, and that the arterial coronary circulation is not anatomically formed of terminal or end arteries. Also the anastomotic circulation is already existent at birth and appears to increase harmoniously with the growth of the coronary tree until full growth is attained When this growth is reached structural modifications commensurate with increasing age are no longer found No difference in intracardiac collateral circulation is noted in relationship to sex. In certain pathologic conditions, the intracardiac anastomotic arterial circulation shows a modification in both the diameter and the length of the communicating channels. In atrophy of the heart, the collateral circulation un goes an involution process, paralle the involution of the intramural system. However in hypertroph



Fig. 4. Intercoronary arterial anastomoses in right hypertrophy of the heart. *Arrow 1.* Anterior descending branch left coronary artery. *Arrow 2.* Right marginal branch. (Female 24 yr old with mitral stenosis.)



Fig. 5. Septal collateral circulation in right hypertrophy of the heart. *Arrow 1.* Posterior descending branch right coronary artery. *Arrow 2.* Circumflex branch left coronary artery. Posterior view. (Male 27 yr old with severe kyphoscoliosis, pulmonary emphysema.)

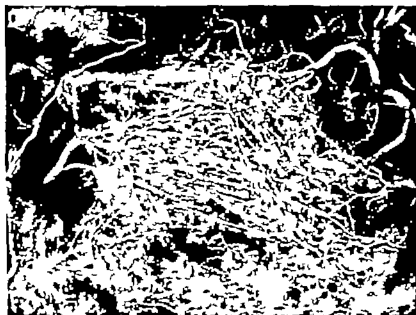


Fig. 6. Collaterals of normal heart in chronic hypoxic disease. (Female, 20 yr. old, with chronic myeloid leukemia.)

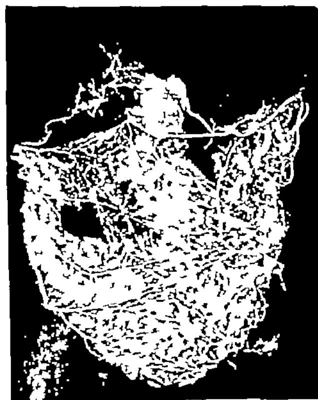


Fig. 7. Occlusion of the first segment, right coronary artery (*arrow*) compensated by numerous enlarged anastomoses of intercoronary type. Posterior surface of the heart. (Male, 79 yr. old, with focal fibrosis of the left ventricle.)

heart the pre-existing anastomoses as well as the other branches show an increase in length and luminal diameter with an apparent increase in the number of the collateral vessels (Figs. 4 and 5) This phenomenon may be defined as a "phanerosis" of the anastomoses. The same "phanerosis" is found in normal hearts of patients with chronic hypoxic diseases (Fig 6) In the heart with obliterative coronary disease, both in the hospitalized patient and in patients dying from sudden unexpected coronary heart death (Figs 7 and 8) the enlargement of the collateral circulation is proportional to the severity of the coronary disease being maximum in those patients in whom multiple occlusions are present. In order to make a comparison of the different groups studied an "anastomotic index" was formulated as follows

$$AI = \frac{(Max\ \phi + Av\ \phi) \times Frequency}{100}$$

where "Max ϕ" or "maximum diameter" in microns refers to the largest anastomotic vessel found "Av ϕ" or "average diameter" is the average of the diameter of the larger anastomoses (greater than 100 microns) and "Frequency" is the frequency of the anastomoses with a diameter greater than 100 microns. This frequency was derived relative to the findings in the normal heart in which the frequency was considered arbitrarily to be 1

On the basis of this formula the behavior of the collateral circulation in the different groups studied was found to have a subnormal value in the atrophic hearts, and a maximum increase in the hearts with multiple occlusions and severe stenosis. There was an intermediate increase in those cases of chronic hypoxic diseases and in hypertrophy of the heart

In particular the enlargement of the normally well-developed intracardiac arterial anastomotic circulation in the human



Fig 8 Collaterals in a case of occlusion at origin of the anterior descending branch left coronary artery (*arrow 1*) and occlusion of the first segment, right coronary artery (*arrow 2*). "Hypervascular area" corresponding to an old infarction of the anterior wall of the left ventricle (Female 70 yr old)

heart was minimal when the luminal reduction was less than 60 per cent was doubled or tripled when the stenosis ranged between 60 and 80 per cent and was maximally increased when the vessel was occluded. The intracardiac arterial anastomotic circulation is independent of the site of the stenosing lesion since a potential source of anastomotic compensation is present in all of the regions of the heart. The collateral development is similar in patients with a history of chronic coronary disease and in those who have died from sudden unexpected coronary heart death[11] with no relationship to sex or age. With regard to the relationship between the increase in the anastomotic circulation and the myocardial damage a more or less equal increase in the anastomotic circulation occurred in cases of occlusion of the coronary artery without myocardial damage, in cases of focal damage in cases of old infarction in cases of acute recent infarction and in cases with associated (old and recent) infarcts. It would appear from this finding that the myocardial damage may be in part if not totally independent of the degree of the anastomotic enlargement, and it is impossible, therefore, to judge the protective function of the collateral circulation in the human heart by the presence or absence of myocardial damage. On the other hand it must be pointed out that in 91 per cent of the cases of occlusion and infarction and in 95.8 per cent of the cases of occlusion and acute infarction a markedly elevated collateral circulation was found. This lends support to the view that without regard to the relationship of age sex, or mode of death in most of the human cases of occlusion a well-enlarged collateral circulation exists far superior to that of the normal heart as a result of the effect of conditions existing prior to the occlusion such as hypertrophy chronic hypoxia, and over all severe stenosing coronary disease. It must be pointed out that in hearts with severe stenosis and/or occlusions the satellite anastomotic circulation may be formed by a large number of relatively small vessels or by a relatively small number of very much enlarged channels. These two different patterns may be explained at least in part if we bear in mind that secondary to the necrosis of the myocardium there is a loss of the intramural branches and therefore also loss of anastomoses. (An avascular area is well demonstrated by the casts in Fig 9.) When this happens an increase in the caliber of the surviving anastomotic channels is expected. Finally it must be said that, in general the variations in distribution of the coronary arteries, and the presence or absence of the third coronary artery have no significance in relation to the anastomotic compensation or to the myocardial damage. The recanalization of occluded vessels, the eventual new formation of an anastomotic vessel at the site of a repairing process (as in the infarcted areas or in the interventricular mural thrombus) or the creation of a new arterial communication by surgery have little if any significance in human pathology because of pre-existing competing anastomoses. Apart from the very rare cases of occlusion of both coronary ostia in aortitis, for which further investigation is required it seems that the extracardiac coronary anastomotic circulation plays no role at all in coronary heart disease. The same conclusion was drawn with regard to the arterioluminal and Thebesian vessels. In our study the cardiac arteriovenous anastomoses were not demonstrated. However in applying the injection and corrosion method we were unable to establish from the cast whether occlusion was acute or old. We were able to confirm only that in most of the cases of occlusion an occlusive type of anastomotic circulation was present which was at all times capable of filling the distal portion of the occluded vessel(s). In other words, in most of the cases when an acute occlusion occurred it occurred in those vessels which had previously been severely stenosed. To confirm this finding and to establish the incidence of the acute coronary occlusion in cases of of myocardial infarction and in cases of sudden coronary heart death histologic studies were undertaken.

"Histologic" study?

Frequently cases of myocardial infarct without coronary occlusion or acute occlusion are reported in the literature. Branwood and Montgomery[4] demonstrated a recent occlusive thrombus in 71 per cent of their cases of recent myocardial infarct, and recent nonocclusive thrombi in 38 per



Fig. 9. Anterior surface of the heart. Typical intramural "avascular" area in a case of recent massive infarction at the peri-septum of the heart. Old occlusion of the second segment, right coronary artery well compensated by extensive anastomotic circulation (red arrows). Arrow: Anterior descending branch, left coronary artery. (Male 50 yr. old.)

cent of their cases of recent myocardial infarct. They speculated that the recent thrombosis may be secondary to the myocardial necrosis. The same results and conclusions were reached by Ehrlich and Shinohara,[5] who demonstrated a 50 per cent incidence of occlusive recent thrombi in cases of recent infarct. They reported that in 26 per cent of their cases the recent thrombosis occurred distally to severe stenosis or old occlusion and assumed that the thrombosis in severely stenosed vessels follows the stasis in compact circumscribed areas of myocardial necrosis. The significance of such cases of myocardial infarct without acute occlusion is of primary importance in the definition and interpretation of the "myocardial infarct" in human pathology.

By the term "myocardial infarct" we generally mean a coagulation necrosis of the myocardium which is secondary to an acute vascular occlusion and is distinguished from other necroses such as myocytolysis that have a different morphopathogenetic pattern.[6]

In our study the selection of cases and the method of investigation employed was as follows:

1. Two hundred eight cases of hospitalized patients of both sexes were selected; the age of the patients varied from 29 to 84 years (average 61 years) and death occurred from acute or recent myocardial infarct.

2. One hundred sixteen male and female subjects were selected; the age range was 20 to 82 years (average 44 years); death was listed as sudden and unexpected and the only pathologic finding at autopsy was a coronary arterioatherosclerosis with or without demonstrable myocardial coagulation necrosis.

3. One hundred twenty-five cases were

studied in which a pattern identical to that in Group 2 was present, but in which the sudden death was not unexpected since the individuals had definite clinical histories of heart disease. The age of the subjects varied from 20 to 90 years with an average age of 48 years.

In each case the extramural coronary arteries and their main branches were studied by transverse serial sections and any occlusion or severe stenosis was examined microscopically. The lumen of the vessels involved by old atherosclerotic processes was measured by a micrometer and the percentage of reduction was calculated when compared to the normal average diameter of these vessels. The site and extent of the myocardial coagulative necrosis was recorded and following the criteria of Mallory and associates[7] and Irniger[8] an attempt was made to correlate the approximate age of the acute or recent thrombosis when either was present. In the three groups examined the absence of an acute or recent occlusive thrombosis was demonstrated in 53 per cent of the "hospitalized" subjects, in 53 per cent of the cases of "sudden unexpected death" and in 54 per cent of the cases of "sudden but not unexpected death."

Because of the difficulty in establishing an accurate histologic evaluation of the age of both myocardial necrosis and thrombus, the figures which we obtained in an attempt to establish the coeval relationship between these lesions must be considered in a broad sense. With this reservation in mind we estimated that in the three groups studied a coeval relationship between the acute or recent myocardial infarct and the eventual co-existing acute and recent thrombus was possible in 23, 22 and 19 per cent of the cases, respectively.

The third important finding was the very high frequency of old severe sclerotic reduction of the vascular lumen which was in excess of 65 per cent and was found at the site of or immediately proximal or distal to the site of the acute or recent thrombus, as follows: in 82 per cent of the "hospitalized" group, in 91 per cent of the "sudden unexpected death" group and in 97 per cent of the "sudden but not unexpected death" group.

Conclusions

The data obtained from these studies have led us to the conclusion that most of the so-called myocardial infarcts in human pathology are not true infarcts according to the general definition of this term and that they cannot be compared to the experimental infarct, which follows an acute occlusion of a normal coronary artery. The fact that in acutely thrombosed vessels there is a high frequency of severe old stenosis or old occlusion generally with well-enlarged collateral circulation would indicate that this collateral circulation is functionally adequate, as demonstrated in both human and experimental cases.[9] A particular hemodynamic condition must exist at the level of the severe stenotic lesion in these rigid tube-like vessels as a consequence of the reduction in the normal proximal flow coupled with compensation by the anastomotic distal backflow. The slowing or hindrance of the blood flow in a portion of the stenosed vessel due to these conflicting factors, might explain at least in part the pathogenesis of the eventual thrombosis. Other concomitant conditions, correlated to the damage of the vessel wall, cannot be ruled out as cofactors in the genesis of the thrombosis. In fact, any cause which is capable of increasing peripheral resistance, such as loss of contractile power, stasis, edema, and stretching of the cardiac wall after extensive myocardial injury, or any cause which is capable of producing a fall in the systemic blood pressure, as in shock, may further aggravate the already critical hemodynamic conditions in the stenosed vessel.

Many theories, including those of microcirculatory alterations,[10] metabolic damage from catecholamines,[11] acute coronary insufficiency,[4] oxygen differential,[12] acute intimal edema, and vascular spasm,[7] have been postulated in an attempt to explain myocardial infarction and coronary sudden death without acute occlusion. However, since in human pathology these are more hypothetical possibilities than proved facts, we would emphasize that the pathogenesis of the myocardial infarct and sudden "coronary" heart death still remains obscure and that such terms as ischemia, anoxia, and acute or chron

ic coronary insufficiency are worthy of discussion. We should especially keep in mind the occurrence of myocardial necrosis without apparent demonstrable interference with the blood flow in some experimental conditions,[19] and we should furthermore, consider the ability of the heart to resist ischemia or anoxic conditions both acute and chronic.[21,22]

Summary

The results and conclusions of a study on the relationship between coronary occlusion and myocardial coagulative necrosis are reported. Five hundred twenty-two human hearts were examined by a plastic injection method which produces detailed 3-D casts of the coronary vessels, permitting a careful study of the collateral circulation. Another four hundred ninety-nine cases were examined histologically and the incidence of the acute coronary occlusion in relation to the age of the myocardial damage and to the pre-existing sclerotic stenosis is reported. The frequency of the true infarct in human pathology is discussed.

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Appraisal and reappraisal of cardiac therapy

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Antianginal drugs
Part V. Monoamine oxidase (MAO) inhibitors

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In 1957 it was noted that iproniazid, a monoamine oxidase (MAO) inhibitor, seemed to decrease the symptoms of angina pectoris in patients given the drug for mental depression. This accidental observation led to further investigation with iproniazid and other MAO inhibitors, but the role of these drugs in angina is still not clear. The MAO inhibitors studied include iproniazid (Marsilid), isocarboxazid (Marplan), phenelzine (Nardil), and nialamide (Niamid). Iproniazid has been withdrawn from the market because it produces hepatotoxicity.

Human pharmacology. All compounds in this group have the property of inhibiting the enzyme monoamine oxidase, which is responsible for the oxidative deamination of serotonin, epinephrine, and norepinephrine. Inhibition of this reaction is believed to lead to an increase in serotonin and catecholamines in the tissues but apparently not in the circulation.

Iproniazid, the prototype of the series, was first introduced as an antituberculous drug and was found accidentally to produce euphoria as a side effect. This led to its use in the treatment of mental depression. The mechanism of its antidepressant action is not known, but it is presumed to be due to a change in cerebral catecholamines.

The pharmacologic basis for the apparent antianginal efficacy is unknown, but the following hypotheses have been considered: (1) the centrally induced euphoria may make angina more tolerable; (2) these drugs may cause coronary vasodilation per se or by the accumulation of either myocardial noradrenaline or serotonin; (4) they may block carotid sinus reflexes; (5) by sympathetic blockade the blood pressure is lowered and the resultant decrease in the work of the heart may relieve angina. A favorable direct cardiac effect would not be anticipated in view of the present concept that high levels of cardiac catecholamines tend to increase the occurrence of angina rather than decrease it. In addition, the hemodynamic effects of catecholamines, such as increased myocardial oxygen consumption, hypertension, and increased heart rate, would also seem likely to increase rather than decrease angina. To overcome these contradictions it has been proposed that MAO inhibitors produce an intracellular accumulation of the hormones, which in turn renders the vascular tissues less sensitive to circulating catecholamines.

These drugs do not seem to prevent the ischemic changes observed in the post-exercise electrocardiogram. This has been used as evidence that the antianginal effect of these drugs is central. In the patient with angina, the tachycardia, hypertension

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and increased cardiac output seen after exercise are decreased significantly by isocarboxazid (Marplan) and pargyline (Futonyl) The latter is a MAO inhibitor *which is recommended as an antihypertensive* drug but has not been reported to be an antianginal drug These drugs can produce significant orthostatic hypotension particularly in patients receiving chlorothiazide or in those with previous myocardial infarction It is possible then that drugs with such actions could affect angina directly despite their lack of effect on the postexercise electrocardiogram

Antianginal efficacy Most of the studies indicating a favorable result with these agents have been of the uncontrolled variety In the double blind studies, the majority report that these agents are equal to a placebo To the best of my knowledge these drugs have not been assayed by controlled studies employing angina producing exercise tolerance tests. This must be done before the final chapter is written on these agents The therapy of angina pectoris is presently so inadequate that we cannot discard potentially useful drugs without adequate testing Pending such studies, however these agents cannot be recommended for use in angina pectoris.

One reason that these drugs have fallen into disfavor even with those who have been impressed by their antianginal efficacy is that they are thought to deprive the patient of the protective warning of cardiac pain since they seem to relieve angina without altering the ischemic pattern in the postexercise electrocardiogram This fear arises from a prevailing but unproved concept that these electrocardiographic changes are the precursor of myocardial infarction Actually in none of the studies with these drugs has an increased incidence of myocardial infarction been observed as might have been expected with an improvement in effort capacity and a simultaneous central blocking of the warning chest pain

Dosage The recommended initial and the maintenance daily doses for these drugs are as follows iproniazid 150 mg (25 to 200 mg) isocarboxazid 30 mg (5 to 40 mg) phenelzine 45 mg (15 to 75 mg) and nialamide 75 mg (25 to 200 mg) The daily dose may be given as a single dose or in divided doses Since there is a cumulative effect, the daily dose is reduced in steps of one half or one tablet as soon as benefit becomes apparent. This is said to require from 1 to 4 weeks.

Side effects toxicity and precautions These agents produce marked potentiation of other drugs. Thus, they should not be used with sedatives or hypnotics alcohol narcotics, hypotensive agents, anesthetics insulin or phenylephrine Since the effects persist after discontinuation of their use it is best to wait a few days before reintroducing any of the above-mentioned agents Such potentiation is particularly hazardous with imipramine (Tofranil) and its analogues

Some of the side effects of MAO inhibitors are reminiscent of ganglionic blockade orthostatic hypotension xerostomia flatulence constipation retention of urine blurred vision and impotence. Dizziness, vertigo headache jitteriness, mania and hypomania weakness fatigue insomnia peripheral edema skin rashes, black tongue, urinary incontinence neuritis spider angiomata and hallucinations have been reported These drugs should be used cautiously in epileptics, since they may heighten the incidence of seizures

By far the most serious potential toxic effect is drug induced hepatitis this can be fatal Accordingly serial tests of hepatic function should be made at reasonable intervals. At the first sign of hepatic malfunction the drug should be discontinued It would seem to be unwise to administer one of these drugs to a patient with a history of liver disease In those with renal insufficiency the dose should be carefully regulated to prevent serious accumulation since the drugs are excreted through the kidneys.

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Platelet thrombosis in experimental renal papillary necrosis

The pathogenesis of renal papillary necrosis has been a topic of speculation for many years. The lesion has been produced experimentally by the use of toxic agents,[1-4] by ureteral obstruction with associated bacteremia,[5] by diet, and by temporary renal arterial occlusion.[7]

Recently in this laboratory papillary necrosis was produced in the rat by the method of Patrick and co-workers by means of a single intravenous injection of fresh pooled human serum the vasculature was studied by means of arterially injected India ink. The findings of these ink tracer studies were correlated with sequential morphologic changes during the development of papillary necrosis observed by both light and electron microscopy. Within half an hour after the injection of serum, platelet thrombi began to form in the vasa recta of the medulla. These thrombi caused vascular obstruction and alteration of the circulation in the medulla and thus prevented filling of the papilla. Medullary necrosis was first noted 8 hours after the injection of serum. Electron micrographs of the vasa recta in the involved area demonstrated endothelial damage within half an hour after the injection of serum. At this time, platelets were attached to some of the damaged endothelial cells and to the denuded vessel walls. The adherence and aggregation of platelets were progressive and led to thrombotic occlusion. Deposition of fibrin was then noted. Heparinization prior to the injection of serum did not prevent the development of platelet thrombi and papillary necrosis but did prevent the deposition of fibrin. Thus it was concluded that platelet thrombi and not the deposition of fibrin accounted for the lesion.

In these experiments with intravenous injection of serum vessel walls were injured chemically. Other investigators have injured vessel walls by physical means and have observed the development of platelet thrombi. Born and co-workers[14] by means of mechanical injury and French and co-workers[15] by means of electrical current. These findings per se are not new. As long ago as 1882 Bizzozero[16] observed platelets adhering to injured vessel walls. However exactly what the serum substance is that damages the endothelial cells remains unknown. Nor do we know why only some endothelial cells of the renal medullary vasa recta are damaged and not others, either at this site or elsewhere in the body.

In man it is not proved but it is possible that platelet thrombosis in the vasa recta may initiate renal papillary necrosis. For example Edmondson and co-workers[18] found hyaline thrombi in papillary necrosis associated with acute pyelonephritis and diabetes mellitus. These hyaline thrombi could have been degenerated platelet thrombi. In those cases of clinical papillary necrosis in which thrombi are not observed it is likely that platelet thrombi nevertheless could have initiated the lesion. We have observed in experimental rat lesions that the platelet thrombi cannot be detected in the later stages of disease. In fact, Patrick and co-workers who were the first to report the morphologic findings after serum-induced papillary necrosis failed to find platelet thrombi. No doubt, they did not detect platelet thrombi because their observations were made 72 hours after the injection of serum when lesions were already well developed. Obviously what is needed—and difficult, if not impossible to carry out—is a search for platelet thrombi in early cases of necrotizing papillitis in man.

Most clinical cases of papillary necrosis are associated with diabetes, obstruction of the urinary tract, or pyelonephritis. However a few are not.[18-20] Of special interest in this regard is phenacetin nephritis. It is one type of papillary necrosis in man which apparently is initiated by a nephrotoxin, and is not associated with diabetes obstruction of the urinary tract or infection. Our experimental rat lesions were similar in that they were initiated by chemical injury and were not associated with these processes. Phenacetin nephritis however differs from serum-induced necrosis in that both the renal cortex and medulla show focal interstitial fibrosis and tubular atrophy.[20-21] Moreover years of phenacetin abuse may elapse before lesions develop. Serum-induced papillary necrosis, on the other hand follows a single injection of serum and has an abrupt onset, and medullary necrosis is followed by inflammation, fibrosis, and tubular dilatation.

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Sudden death and the oxygen-conserving reflex

[illegible]udies of cardiovascular and metabolic adaptations [illegible]uring diving may offer an [illegible]pproach to the under[illegible]anding of unexplained [illegible]udden death. As early as [illegible]870 the French physiologist Paul Bert observed marked bradycardia in di[illegible]ing ducks. A few years later his compatriot, Charles Richet, recognized that bradycardia due to diving was part of an oxygen-conserving reflex that enabled [illegible]nimals to survive under water three times as long as their body's supply of oxygen would allow under ordinary apneic conditions.

In recent years the reflex has been documented in a variety of reptiles, birds, [illegible]nd mammals, including man. The elements of the reflex have been identified as follows:

Circulatory: (1) bradycardia, (2) decreased flow of blood to skin and viscera, (3) increased arterial pressure. *Metabolic:* (1) fall in blood pH, (2) rise in lactic and other organic acids, (3) rise in blood CO[illegible] and K. Mediated at the level of the brain stem, the reflex may be elicited in decerebrate preparations. In lower forms such as the alligator the reflex is highly automatic and predictable, occurring whenever the animal's head is placed under water. In higher animal forms, however, it is subject to considerable modulations by higher centers of the brain. Thus in the porpoise the mechanism governing the reflex depends on the animal's intent, so that during playful dipping in and out of the water there is no bradycardia. At the beginning of a real dive, however, an immediate bradycardia occurs as the head is submerged. In man the reflex, such as it is, is subject to many modulating forces, acting presumably through cortical connections. The reflex may be inhibited, facilitated, or even induced in response to symbolic stimuli: words or events with emotionally charged significance to the individual concerned. Thus bradycardia and the other associated changes of the oxygen-conserving reflex failed to accompany immersion of the face when the subject was distracted or harassed.[3] On the other hand, during intense anxiety or fear the reflex was actually facilitated, all of the changes being accentuated. Indeed, stressful situations were found to be capable of initiating the reflex without immersion of the face in water. Thus the bradycardia of vasovagal fainting was shown to be accompanied by slower respiration and a rapid rise in the serum concentration of lactic acid and potassium, the manifestations of anaerobic metabolism which characterize the oxygen-conserving reflex.

In experiments with rats made to swim to exhaustion, Richter showed several years ago that bradycardia with ultimate cardiac arrest, rather than drowning, provided the mecha[illegible]ism of death.[7] Richter could cause the rats to die much sooner by simply cutting off their mustache hairs, or vibrissae, their principal source of sensory information. On the other hand, rats removed from the water just prior to death were able to swim about and survive for a much longer time when placed in the water

the following day. It seems to be difficult to escape the inference that Richter demonstrated the survival value of hope and the potentially lethal nature of situations which rob the organism of support from his environment. Richter suggested that the sudden death of ostracized persons in primitive societies, voodoo death, might also be attributable to a vagal mechanism in reaction to loss of hope. Such a response becomes more understandable when seen as an essentially protective conservative reflex, inappropriate and useless under the circumstances, but crudely adaptive nevertheless.

Sudden deaths occurring in civilized society are usually attributed to myocardial infarction although often enough no necrosis of the myocardium is found. There is no means of proof in retrospect, but one can reasonably suspect that a host of bizarre sudden deaths, deaths from "fright," unexplained deaths in swimming pools, and "crib" deaths may be attributable to an overexuberant oxygen-conserving reflex. It is intriguing also to speculate that this mechanism may contribute to sudden death in angina pectoris and myocardial infarction itself. A quickly elicited adaptive maneuver to conserve oxygen might be considered to be appropriate in the face of myocardial ischemia. However, the slight acidification of the blood and the elevation of serum potassium accompanying the oxygen-conserving reflex would presumably, together with the local products of ischemia, increase the likelihood of fatal arrhythmia. The association of intense anxiety or fear with an anginal attack or infarction might thus accentuate or even initiate the oxygen-conserving reflex—an essentially protective mechanism that may prove to be lethal if inadequately balanced by opposing forces.

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High-altitude pulmonary hypertension

Some degree of pulmonary hypertension appears to be inevitable at high altitudes. The condition, however, has a comparatively recent history. A moderate degree of pulmonary hypertension was first reported among permanent residents of the Peruvian Andes by Rotta and his colleagues[1] in 1956. These findings were confirmed 7 years later by Simon and Peñaloza and their colleagues. Vogel and his colleagues[3] reported the condition from the United States in 1962. Individuals suffering from chronic mountain sickness or Monge disease have been found to have a much higher degree of pulmonary hypertension.

As with high altitude pulmonary edema, the altitude at which vulnerability occurs seems to be related to the local snow line or temperature. In the Peruvian Andes, Hurtado[4] reported the condition in individuals born and raised between altitudes of 13,120 and 14,760 feet. In comparison, the altitude which predisposes to vulnerability is 11,500 feet in the Himalayas and 10,150 feet in the United States.

Pulmonary hypertension may remain indefinitely asymptomatic in local residents at 11,500 feet until they move to altitudes a thousand or more feet higher or undertake employment involving severe physical exertion. Such a breakdown occurs within 6 to 24 months among local residents in the Himalayas.

In temporary residents who go to the Himalayas from sea level the symptoms of pulmonary hypertension begin after a stay of 5 to 42 months at high altitude. After the initial onset of the disease, periodic returns to sea level for 2 to 3 months once a year do not alter the picture. The hypertension either continues to persist at sea level or, if it abates, it reappears within 2 to 3 weeks after the individual returns to high altitude.

Pulmonary hypertension may have an acute onset in association with high-altitude pulmonary edema. It may persist after all clinical evidence of pulmonary edema has disappeared.

The minimum requirements for a diagnosis are dyspnea on effort, chest pain, accentuated second pulmonary sound, clockwise rotation, and prominent pulmonary artery on x-ray examination. To be of significance the dyspnea on effort must be considered in relation to the effort to which the individual was already accustomed. An accentuated second pulmonary sound is often found in associ-

ation with increased pulmonary blood volume without pulmonary hypertension.

About 10 per cent of temporary residents with pulmonary hypertension develop right ventricular failure with elevated jugular venous pressure, enlarged and tender liver, ascites, edema, [illegible] dyspnea. Some caution, however, is necessary in diagnosing right ventricular failure. At high altitude the lung volumes increase, the individual becomes broad chested, and his diaphragm moves down. As a result of the downward movement of the diaphragm the liver may become palpable and therefore its presence does not necessarily [illegible] right ventricular failure. When enlargement of the liver is due to right ventricular failure it is enlarged as well as tender, and the jugular pressure [illegible] increased.

When temporary residents return [illegible] sea level, evidences of high-altitude pulmonary hypertension usually disappear within about 3 [illegible] on an average. A few individuals who [illegible] likely to be permanently disabled. In [illegible] the clinical course of the disease is not affected by the administration of such drugs as tolazoline, guanethidine, reserpine, nitroglycerin, or prenylamine lactate. If the patient has edema, he will be benefited by the use of diuretics, but dyspnea and chest pain will remain unaffected.

The following are considered to be absolute indications for return to sea level if permanent disability is to be avoided: dyspnea with encroachment on effort to which the individual was previously accustomed, chest pain of the anginal type, a split pulmonary sound especially if associated with a pulmonary systolic murmur, a prominent pulmonary artery on x-ray examination, and ECG changes of Grade I right ventricular hypertrophy (dominant R in Lead V_1 or dominant S in Lead V_6), right ventricular strain (T inversions in Leads V_1-V_3), right bundle branch block (slurred R in Leads V_1-V_2 and V_{3R}-V_{4R}), and QRS interval above 0.10 second.

The pathogenesis of high-altitude pulmonary hypertension is far from clear. Rotta and his colleagues found an inverse correlation between chronic hypoxia and pulmonary arterial pressure. However, with acetylcholine and oxygen therapies, pulmonary hypertension decreased only 15 to 20 per cent. Apparently, therefore, hypoxia does not affect the pulmonary arterial pressure directly.

The pulmonary vascular bed is greatly increased in healthy residents of high altitudes, and there is thickening of the muscular layer of the small pulmonary arteries and muscularization of the pulmonary arterioles. Peñaloza and his colleagues[3] attributed high-altitude pulmonary hypertension to increased pulmonary vascular resistance resulting from widespread narrowing of the lumen of the pulmonary blood vessels on account of these changes. However, since pulmonary hypertension in these cases is not affected by oxygen therapy, the effect of these changes, if any, could only be mechanical. It is more likely that these changes are secondary to pulmonary hypertension. In the absence of these changes an increased pulmonary vascular bed may be found in association with an increased pulmonary blood volume, but without pulmonary hypertension.

Polycythemia per se does not seem to predispose to pulmonary hypertension. Pulmonary hypertension may be present without polycythemia, or it may persist after the red blood cell count has returned to normal after the individual has returned to sea level.

Although we may try to implicate pulmonary vasoconstriction, increased pulmonary blood volume, and polycythemia in the pathogenesis of high-altitude pulmonary hypertension, we cannot explain on those bases the slow disappearance or persistence of pulmonary hypertension after the individuals return to sea level. There is evidence that the pulmonary hypertension in such cases is the result of organic changes. In the acute pulmonary hypertension of high-altitude pulmonary edema there is occlusion of the alveolar capillaries and small branches of the pulmonary artery by lodged red cells[5] and fibrin thrombi.[18] In high-altitude pulmonary hypertension, occluding thrombi are found in small blood vessels. Some of these thrombi show evidence of recanalization. This would suggest that after the individual has returned to sea level, high-altitude pulmonary hypertension resolves slowly through recanalization of thrombi and continued blocking of blood vessels leads to its persistence.

The deposits of fibrin in the alveolar capillaries and branches of the pulmonary arteries are not found in isolation. Similar fibrin thrombi are observed in the glomerular and peritubular capillaries in the kidneys, and also in the sinusoids of the liver. There may also be intra-alveolar deposition of fibrin. These widespread deposits of fibrin suggest that at high altitude there is a breakdown of the fibrinolytic enzyme system and that the equilibrium between the formation and the dissolution of fibrin is upset.

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The second heart sound in pulmonary embolism and pulmonary hypertension

The traditional auscultatory signs of pulmonary embolism are accentuation of the pulmonic component of the second heart sound, a systolic murmur and scratch over the pulmonary artery, and occasionally a loud continuous murmur. Since 1960, we have studied phonocardiographically the effects of pulmonary embolism and pulmonary hypertension. In acute massive embolism and in severe chronic blockage of the main pulmonary arteries, the second heart sound is usually very widely and often fixedly split in the absence of any other detectable cause. When borderline, the abnormal splitting can usually be increased and fixed by mild exercise. The "second heart sound sign" has been helpful in finding cases of massive thromboembolism previously missed, in evaluating the course of patients treated medically, and, recently, in deciding how urgently pulmonary embolectomy is needed. Embolism to even two or three segmental pulmonary arteries in the absence of pre-existing disease of the pulmonary vascular tree has no effect on the heart sounds. Yet in 18 proved cases of massive acute pulmonary embolism or chronic pulmonary artery thrombosis with pulmonary hypertension, the second heart sound was abnormally split in expiration; respiratory mobility was usually much reduced but not always eliminated unless the patient had rather severe right ventricular failure. Because of accentuation of the pulmonic component of the second heart sound, the wide separation was usually easy to appreciate clinically. At rest, in the least striking cases, the split was only 0.03 second in expiration, opening further on inspiration. In the worst cases the split was as much as 0.075 second in expiration and quite fixed. On several occasions the delayed pulmonic component was mistaken for an opening snap. In one case of pulmonary artery thrombosis an erroneous diagnosis of atrial septal defect had been made because of the abnormal second heart sound and dilated central pulmonary arteries. Standing tended to close the abnormal split but never obliterated it. The effect of exercise (doing sit-ups on the examining table) was most distinctive. The increment of splitting was usually most marked during tachycardia immediately after exercise but often persisted even when the heart rate had slowed toward resting levels. If the heart rate was slowed by vagal stimulation immediately after exercise, the splitting became even more striking. During effort, the cervical venous pressure rose and giant A waves were common. Control experiments both with normal subjects and with patients who had recovered from acute pulmonary embolism showed that exercise does not increase splitting of the normal second heart sound. Hyperventilation likewise failed to reproduce the type of change observed during the acute episode. During convalescence from acute massive pulmonary embolism in 5 cases, serial phonocardiograms showed gradual merging of the two estranged components of the second heart sound. The return to normal took from 36 hours to 6 days. During the recovery period and sometimes for 1 to 2 weeks afterward, an abnormal response to exercise could be obtained.

In *chronic* obstruction of the pulmonary arteries the hemodynamic factors most readily correlated with the degree of splitting of the second heart sound were the height of the pulmonary arterial systolic pressure and the presence of an elevated right ventricular diastolic pressure at rest. In patients with pulmonary arterial pressures in the systemic range and clear-cut right ventricular failure, the split was always 0.05 second or more at rest and easily increased with mild exercise. One patient with complete occlusion of the right pulmonary artery of 15 years' duration had normal pressures and normal splitting even after exercise. Few hemodynamic data are available in the cases of acute pulmonary embolism. In cases of the widest splitting, right ventricular failure, as assessed by meticulous observation of the neck veins, was usually present or could be brought out by exercise.

By contrast, extreme splitting of the second sound is rarely encountered in other causes of pulmonary hypertension and right ventricular failure. This is notably true of rheumatic heart disease. Primary pulmonary hypertension and small repeated peripheral pulmonary emboli also often do not produce comparable splitting in spite of gross accentuation of the pulmonic component. In 3 cases in which the pulmonary arterial pressure was at systemic levels, the second heart sound was split in expiration by only 0.02 second, widening, however, with exercise to a fixed 0.035 second. Thus, compared with block of somewhat larger pulmonary arteries, the changes were similar in direction but of much less magnitude. Severe Eisenmenger syndrome secondary to ventricular septal defect may be a special case. As previously noted by Leatham,

the second heart sound usually seems to be unnaturally pure; often the absence of respiratory splitting (present in all normal children) has been a *useful diagnostic clue*. Neither *exercise nor the* post-Valsalva overshoot is capable of separating the tightly fused components. Here the ventricles behave almost as a common ejection chamber discharging into both pulmonary and systemic circuits which have similar resistances to flow. Under these circumstances any prolongation of right ventricular systole would keep the aortic valve open as long as the pulmonic.

As noted by Aygen and Braunwald, splitting of *the second heart sound can provide a useful way* of detecting differences in the ejection time of the two ventricles. With phonocardiograms quite meaningful indices of ejection time may be obtained—although direct measurement of right ventricular ejection is not possible. Experimental studies on the left ventricle have shown that the duration of ejection can be *increased* by augmented stroke volume, bradycardia, a grossly elevated resistance to outflow, hypothermia, and myocardial *failure*; *ejection time is shortened* by a decreased stroke output, tachycardia, and inotropic catecholamines. Yet in the isolated nonfailing left ventricle ejection time is not prolonged by a considerably increased aortic pressure,[5] and Weissler and associates found that left ventricular ejection time was not increased for stroke volume in nonhypotensive *left ventricular failure. Thus* when stroke output is reduced, prolongation of ejection may require a peculiar combination of increased resistance and ventricular failure. Unfortunately, we know of no comparable studies on the right ventricle.

Our observations show that in acute massive pulmonary embolization left ventricular ejection time is shortened. Angiocardiograms suggest that this is probably due mainly to a considerably decreased stroke volume, although the discharge of catecholamines secondary to the catastrophe *may* also contribute. By contrast, the right ventricular ejection time, especially at slower heart rates, may appear to be only modestly prolonged; however, in view of the greatly curtailed stroke volume, the rate of ejection must be drastically reduced. Thus splitting in acute pulmonary embolism appears to be due to a conspiracy of factors: *a full, obstructed* right ventricle with some degree of failure and a long ejection time relative to its small output; an empty left ventricle rapidly ejecting its small ration of blood. In chronic pulmonary artery obstruction, since cardiac output is better maintained, prolongation of right ventricular ejection is more easily *appreciated as the prime cause of abnormal splitting*. Here inspection of pressure curves has shown that the prolongation is mainly of ejection itself rather than of the pre-ejection phase. The commonly observed difference between thromboembolism and other causes of extreme pulmonary hypertension and right ventricular failure appear to need further explanation. *In analogy with thromboembolic cases* we considered not only the delayed pulmonic sound in valvular pulmonary stenosis (in which the increased ejection time is partly the result of the low closing pressure applied to the valve), but also the abnormal splitting of the second heart sound encountered in coarctation of the pulmonary artery and after the banding procedure for ventricular septal defect.[8-10] Perhaps exceptional prolongation of right ventricular ejection in proportion to output *is most importantly* due to *the peculiar rigidity of* the obstruction to flow.

Whatever its mechanisms, the clinical usefulness of the second heart sound sign has been established in a variety of circumstances. Frequently it was the catalyst which led to the synthesis of other elements into an immediate diagnosis. Absence of the sign should make one hesitate to advise pulmonary embolectomy. Yet we do not mean to imply that the second sound is abnormally split in all *cases of significant pulmonary* embolism. Emboli may be quite important, and in some circumstances even life threatening, without being massive. In fact, during the period of the study nine ligations of the inferior vena cava have been performed on patients with normally split second heart sounds. The presence of bundle branch block or any other cause of wide splitting obviously vitiates the sign.

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Book reviews

THE LUNG CIRCULATION. Vols. I and II. By Domingo M. Aviado, M.D., Associate Professor of Pharmacology, University of Pennsylvania School of Medicine, Philadelphia, Pa. New York, 1965, Pergamon Press, Inc., 1,405 pages. Price $30 per set.

These two volumes on the circulation of the lungs represent a great deal of work. Dr. Aviado presents an extensive and critical review of the literature. The first volume is concerned with the physiology and pharmacology of the circulation of the lungs, and the second volume presents the pathologic physiology and therapy of disease states. The author presents his interpretation of the data in the literature. He does not merely summarize publications, a practice common in the noncritical reviews. In these 1,400 pages, Aviado discusses very well the physiology and pharmacology of the circulation (pulmonary and bronchial) of the lungs. There is an extensive bibliography at the end of each chapter and a very good author index at the end of the two volumes. The reader who may differ in opinion concerning details of physiology, pharmacology, and therapy can locate the original papers for careful study. The two volumes represent a good supplement to the handbook publications of the American Physiological Society on respiration, as well as a supplement to the handbook volumes by that Society on the circulation. The two volumes by Aviado are well organized, well illustrated, and well written. The reader, of course, must evaluate the discussions of the specific problems in these two volumes in light of his own interest and studies, but he will find the concepts and interpretations of the author clearly expressed. This is an advantage, especially when dealing with such complex and little understood aspects of normal and abnormal cardiovascular physiology and pharmacology as the circulation to the lungs.

ERKRANKUNGEN DER AORTA UND IHRER ÄSTE. (MALADIES DE L'AORTE ET DE SES BRANCHES). International Symposium, Bern, Switzerland, Nov. 13 and 14, 1964. Basel and New York, 1965, S. Karger. 247 pages.

The diseases of the aorta and its major branches form a heterogeneous group of conditions with different causes and clinical manifestations. The problem of making an exact diagnosis and treating a given case calls for specialists from many medical fields.

This symposium was a meeting of representatives of various medical specialties: pathology, internal medicine, surgery, radiology, neurology, and others. Each of three major divisions takes up the aortic arch syndrome, arterial disturbances of intestinal blood supply, and renal arteriography. For each division, the authors survey current knowledge, describe diagnostic and clinical difficulties, and discuss methods for diagnosis and treatment. The articles are short and clearly delineate the problems. Some overlapping exists, but it is only slightly objectionable. More serious is a frequent lack of correlation between clinical syndromes and pathologic anatomy. The reader is often not certain which disease of the artery is being discussed. In spite of an introduction on the pathologic anatomy of the aorta and its major branches, one misses a better description of the anatomic changes in each disease. Since atherosclerosis is the most frequent of these diseases, a better and more up-to-date survey should have been given this topic.

For the clinician, the book is excellent as an introduction to diseases of the aorta and the main branches. The lists of references are good.

BIOPHYSICAL MECHANISMS IN VASCULAR HOMEOSTASIS AND INTRAVASCULAR THROMBOSIS. Edited by Philip N. Sawyer, M.D., New York, 1965, Appleton-Century-Crofts, Division of Meredith Publishing Company. 379 pages. Price $8.95.

This compendium summarizes the symposium concerning thrombosis, hemostasis, and interfacial physical phenomena. The papers are concerned with (1) electrokinetic phenomena, (2) relationship of electrochemical phenomena to the vascular tree, (3) rheology of blood flow, (4) bioelectric phenomena, surface phenomena, blood clotting and thrombosis, and (5) electrochemical surface physics and insight into construction of a suitable vascular interface. This is a collection of excellent papers on subjects too often neglected in the physiologic consideration of blood flow, clotting, and other circulatory phenomena. The compendium not only presents known facts, but provides many challenging ideas for new studies. The discussions and the bibliographies appended to the papers are good, and the round table on the etiology of intravascular thrombosis is interesting. This is an excellent book. It reveals the complexities of the circulation and the control of clotting and thrombus formation.

Books received

DRUGS OF CHOICE, 1966-1967. Edited by Walter Modell. St. Louis, 1966, The C. V. Mosby Company. 969 pages. Price $16.75.

MANAGING YOUR CORONARY. By William A. Brams, ed. 3. Philadelphia, 1966, J. B. Lippincott Co. 175 pages. Price $3.75.

Announcements

STOUFFER PRIZE The largest medical prize in the world has been posted to track down the cause prevention and treatment of hardening of the arteries and high blood pressure the two most serious threats to human life This prize of $50,000 together with a medal and citation will be awarded annually by the Vernon Stouffer Foundation. This new Stouffer prize is more than the world-famed Nobel prize in medicine, and far more than the coveted Lasker award which is the largest such prize given in the United States. The prize-awarding committee will be named soon.

A course in INTERPRETATION OF COMPLEX ARRHYTHMIAS will be given at Michael Reese Hospital and Medical Center by Louis N Katz M D Richard Langendorf M D and Alfred Pick M.D This is an advanced course intended for experienced electrocardiographers only The class will meet daily from 9 A.M. to 5 P.M. Dec 5 through 10 1966. Registration is limited to 30

Further information and a copy of the lecture schedule may be obtained from the secretary Cardiovascular Institute Michael Reese Hospital and Medical Center 29th St. and Ellis Ave. Chicago 16 Ill.

MEDICAL RESEARCH GRANTS AND FELLOWSHIPS: The Life Insurance Medical Research Fund has announced *Sept 15 1966* as the deadline for receipt of applications for grants in aid of medical research to become effective July 1 1967 These grants are made to nonprofit institutions for support of basic research in physiology biochemistry and other fields related to medicine Further information and application forms may be obtained by interested investigators from the Scientific Director Life Insurance Medical Research Fund 1030 East Lancaster Ave Rosemont Pa 19010.

The Fund also offers Medical Scientist Fellowships to medical students willing to prepare for careers in teaching and research by securing both the M D and the Ph.D or its equivalent The Fellowships offer a maximum of 6 years of aid Fellowships can be activated at various stages of the M D Ph D training Each school of medicine is invited to make two nominations for aid to begin July 1 1967 Deadline for receipt of applications from deans offices is *Oct. 1 1966* Further information can be obtained from deans in schools of medicine.

CLINICAL TRAINING The National Heart Institute announces the establishment of a new additional training grant program for the support of clinical training in areas related to cardiovascular disease.

Graduate clinical training grants are awarded to nonprofit institutions to provide advanced clinical training in disciplines relating to cardiovascular disease. These grants are intended to establish and extend specialized clinical cardiovascular training programs in order to increase the number of facilities providing scholarly training and instruction in these areas, particularly in regard to methods and techniques that have resulted from research advancements. The program is aimed at meeting national personnel shortages by increasing the number of individuals having special competence in matters relating to diagnosis, prevention and treatment of cardiovascular disease. The program is not intended to support routine clinical residency training

Inquiries regarding this program may be directed to the Training Grants and Awards Branch of the National Heart Institute, Extramural Programs.

AN INTERNATIONAL SYMPOSIUM ON SELENIUM IN BIOMEDICINE will be held at Oregon State University Corvallis, Ore., on Sept. 6-8 1966.

For information, contact: O H Muth, D V M Symposium Chairman Nutrition Research Institute Oregon State University Corvallis Ore. 97331

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